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Linkage of Body Build with Sex, Eye Color, and Freckling

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INTRODUCTION

THE present paper represents an attack on several apparent obstacles to the genetic analysis of many traits of long-standing interest to the anthropologist. Physical anthropology, with its essential interest in the normal common variations of the human species, has been so far largely disappointed in the help offered by genetics. The geneticist, interested in the development of precision within his own discipline, selects most naturally for study those traits which offer the least ambiguity of phenotype; traits which are discrete and definite, falling into natural categories rather than vague continuous distributions, simply rather than multiply determined, with perfect or nearly perfect penetrance, and relatively immune to environmental modification Unfortunately, many traits which are included in the field of physical anthropology because of their known racial, regional and individual variation are of such a nature that to compare them with the above list of qualifications is absurd. Particularly is this true in regard to variations in the size and shape of the body or of parts of it.

From the genetic point of view the traits selected for study in this paper may appear to represent a deliberate choice of difficulties. Body build, the trait of primary interest, has just the characteristics the geneticist abhors: a wide continuous range of distribution with a typical normal curve, and a known susceptibility to environmental influence by difference of nutrition. Yet with all its difficulties, body build is only a typical example of the traits the anthropologist deals with and wishes if possible to deal with genetically. The other traits considered (with the exception of sex, which fortunately presents unequivocal phenotypes) are likewise, though to a lesser degree, resistant to the type of classification which precise genetic work demands.

The addition of the linkage issue to the already sufficient difficulties of dealing with a metric morphological trait may appear at first glance to invite failure. Actually linkage offers the best opportunity of analyzing a trait multiply determined, since the multiple factors may be distinguished from one

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another by their different linkage relations. To state that the size of the body or of any part of it is determined by the additive effect of several genes will in fact never be more than an admission of failure until it is possible to identify these summatively acting factors by their several places in the chromosomes. Linkage thus offers an escape from the genetic confusion inherent in multiple gene determination.

In passing, it should be noted that the genetic analysis of metric traits can be unduly discouraged by erroneous ideas about their probable determination, due to a mistaken concept of the normal distribution. Such traits in general appear to follow a "normal" curve, which is theoretically defined as the resultant of many equal independent factors. However, a curve almost

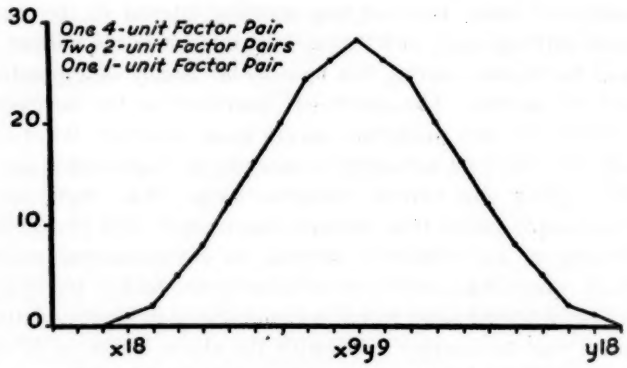

FIG. 1. Graph of the expansion: $(x^4 + y^4)^2\ (x^2 + y^2)^4\ (x + y)^2$.

indistinguishable from a normal distribution may be produced even though the determining factors are very unequal in their effect (Yule, 1932, pp. 306–307). In figure 1 is given, by way of example, a distribution curve constructed to represent a case in which one pair of factors is responsible for nearly half the determination of a metric trait. In such a case the genetic isolation of the major factor need not be difficult, though the appearance of the curve mimics closely the distribution which would result from a large number of small *equal* factors and which would, indeed, resist genetic analysis. Experiment with various expansions of the above type shows that in general it is not till a single factor pair takes over more than half the determination of a trait that any abnormality of the distribution curve becomes either visible to the eye, or susceptible of statistical proof except in large bodies of data.

Two important corollaries should be mentioned. First, the non-equality of causal factors, provided the curve produced is at least pseudo-normal, does not appreciably alter the significance of the standard deviation and associated

statistical measures as they have been used to determine whether two groups are possibly samples from an identical population. Second, non-equality of factors does affect the probability of evolutionary changes resulting from chance gene loss in small isolated groups, making possible more marked and rapid changes than would otherwise occur.

MATERIALS AND METHODS

Measurements, Indices, and Observations

The individuals who served as subjects for this study are the same series reported in an earlier paper (Brues, 1946) dealing with the heredity of eye color. Three hundred persons of both sexes were included, a nearly random sample of the various white stocks resident in New England. The only selection exercised was on the basis of fecundity, since it was desired to obtain as many siblings as possible per family. From 83 families, 466 sib-pairs were obtained. The minimum age set for subjects was 18 years.

Of the various data collected on these subjects, the following are pertinent to the present paper:

Height was taken by standard technique with an anthropometer graduated in millimeters, the subjects being always without shoes.

Weight was recorded as stated by the subjects, since conditions did not permit taking scales to the subjects' homes as part of the equipment. All subjects appeared to be interested in and familiar with their weights, and there is no reason to believe that their statements of their usual weights were greatly in error. Any inaccuracies in this respect would of course tend to conceal true correlations which might be present.

Body Build, for purposes of this paper, is measured by the ratio of height in inches, divided by the cube root of weight in pounds. Any of the various "build" indices, based on the various powers of these two measurements, could have been used; one advantage of this particular one is that it gives virtually identical mean values for males and females. For the reader's orientation it may be pointed out that a one unit difference in this index signifies, in the vicinity of the average male range, a difference of 38 pounds, or about 24 per cent, in weight, for a given height. Hence we will deal largely with fractional values of this index.

Iris Structure gave no positive results in linkage tests but is listed in tables 2 and 6. It is classified according to the system developed in an earlier paper (Brues, 1946), where the types are fully described and illustrated. Smooth designates an iris of dark coloring in which no crypts or atrophic areas are present. Cryptose designates an iris with irregular relief due to atrophy of the anterior pigment-bearing layer; this type presents many color varieties.

Scalloped designates an iris with marked atrophy of the anterior layer which may be somewhat pigmented but probably never really dark.[1] These terms are difficult to apply and may be misleading in many instances.

Eye Color is also classified as in the previous paper. The only distinction used in the present study is that between Light and Intermediate color in irides not of Smooth structure. Light comprises blue and gray, Intermediate the mixed shades and some browns.[1] These two show a sex-linked inheritance, with Light recessive to Intermediate.

Freckling was judged subjectively, and is an imperfect observation, being subject to change with exposure to the sun as well as to inconsistencies of judgement by the observer. For purposes of analysis, three grades of freckling are recognized: absent, few, and many. The latter class includes a wide range, with some rare extremes of cutaneous variegation. The non-objective nature of this observation appears less alarming after it has been found that the data give rise to some excellent correlations.

Four other traits gave no positive results in linkage tests but are listed in tables 2 and 6:

Hair Color—brown records the amount of brown pigment in the hair without regard to the presence or absence of red pigment. A three-fold classification has been used in the analysis: Dark Brown (including black), Medium Brown, and Light Brown (including fair).

Hair Color—red records the amount of red pigment visible; this observation is omitted in the case of dark brown hair, but medium and light brown shades have all been classified as either Red or Non-Red.

Hair Form is classified as Straight, Low Wave, or Deep Wave (including curly).

Ear Lobe Attachment is classified as Free (the lowest point of the lobe lying below the juncture of lobe and cheek), Attached (the lowest point of the lobe lying at about the level of the juncture of lobe and cheek), or Soldered (the lower border of the lobe forming a continuous line passing down and forward to the juncture).

Determination of Linkage from Sib-Pairs

Methods of determining genetic linkage by comparison of siblings with one another, without the use of data concerning the parents, were developed by Penrose (1935, 1938). These methods offer great practical advantage for the study of linkage in man. They are based on the fact that if two siblings receive the same chromosome from a parent, there is an increased probability

[1] To simplify the grouping of the 1946 paper, 'striated' has been included under Smooth, 'eroded' under Cryptose, and 'ridged' under Scalloped; in color classification, Yellow-Mixed, Brown-Mixed and Cryptose-Dark have been combined as Intermediate.

that the siblings will be phenotypically alike in any trait determined or influenced by a gene located in that chromosome. Thus ultimately a correlation is established between sibling likeness in one trait and sibling likeness in a second trait genetically linked to the first.

In the sib-pair method, the determination of linkage between multiply determined traits proceeds in the same way as if the traits were simply determined; the results, however, may be expected to be much less clear. The correlation of phenotype with any particular one of the chromosome pairs involved will become increasingly poorer with the increase in number of factors involved, and so of course will the correlation of one phenotype with another. The decrease in correlation means that a larger number of cases will be required in order to prove that a statistically significant relationship exists.

The statistical handling of sibling differences in metric traits requires some consideration. The most obvious measure of central tendency for sibling differences—the arithmetic mean—has not been used in this analysis. Such a figure is mathematically inappropriate, since the true mean of sibling differences is zero; zero is in fact the commonest or modal value and the center of the distribution curve, with plus and minus values (the sign being merely a function of the order in which the siblings are considered) ranged symmetrically on either side. Consequently the measurement of sibling difference is a measurement of dispersion from a mean rather than of the mean itself. The concept of the mean sib difference as zero may be more readily understood if we consider the problem of comparing brother-brother differences with brother-sister differences in a trait such as stature which has a large sex difference. The arithmetic mean of sib differences will not represent the same thing in the two cases; in the second case it will equal the mean difference between the sex; in the first case, where no such mean difference exists, it is merely a crude measure of dispersion. Graphically, the distribution of sib differences is best depicted as half of a normal distribution, or more exactly, a distribution curve folded back on itself, with plus and minus values combined (or, where a mean sex difference is involved, values equally above and below the mean). Mathematically, the best measure of the difference between siblings is a standard deviation taken from the mean of zero.[2] The use of this measure facilitates the comparison of mean family likeness with the degree of likeness expected in the case of linkage. (For details of calculation see Appendix I).

Since the standard deviation squared (often called variance) increases in direct ratio to the amount of causal variation present, it is doubled when the differences between pairs of individuals drawn at random from a series are used for its calculation instead of the differences between each individual and

[2] Since this is a standard deviation rather than a mean, its standard error is derived by dividing by $\sqrt{2N}$.

the mean. It also follows that the variance of differences between sibs will be (barring non-genetic factors, dominance effects, etc.) half of the variance which would be derived by tabulating difference between pairs of unrelated individuals. The basic element of variance here is the probability that two genes of the same locus, drawn at random from the population, will differ from one another; this is of course equal to the probability that two corresponding genes of two unrelated individuals will differ from one another. In the case of siblings, however, there is always a fifty percent probability that any particular gene received by the first sibling will also be received from the same parent by the second sibling. Hence, where the change of divergence between unrelated individuals is p, the chance of similarity q, the chance of divergence between siblings is $\frac{p}{2}$, the chance of similarity $\frac{1}{2} + \frac{q}{2}$. The total variance between siblings will therefore normally be half that between unrelated individuals, regardless of the number of genetic factors acting.

If a definite linkage is present, sib-pairs selected for similarity or difference in one trait will show a correspondingly smaller or greater variance in a linked metric trait, as compared with the variance of all sib-pairs. If it were possible to select from the total group of sib-pairs those pairs in which likeness was complete in respect to a given chromosome pair, and if a certain metric trait were completely determined by factors present in that chromosome, it would be possible to isolate a group of sib-pairs with a zero variance in the metric trait. If other factors are involved, either non-genetic or located in other chromosomes, the variance of sib-pairs selected for similarity in a given chromosome pair will be reduced to the amount due to those other factors. In practice, of course, it will be impossible to select the one-quarter of our sib-pairs which are alike in respect to both of a pair of chromosomes—at least not by use of one trait alone. Only a battery of traits known to be present in the same chromosome could identify the chromosomes accurately enough for this purpose. Consequently, sib-pairs selected for similarity in one trait will normally show only a moderate reduction of variance in a linked metric trait, the exact degree of reduction depending on many causes.

Sib-pairs may be selected for chromosome difference more easily than for chromosome similarity, since, though like genes may be present in chromosomes of different origin, unlike genes cannot be found in chromosomes of the same origin unless mutation has taken place. The mathematical limit of variance in sib-pairs successfully selected for a double difference in respect to a given chromosome pair is very simply determined. *The variance of a group of sib-pairs so selected cannot be more than the variance of pairs of unrelated individuals.* The sib-pairs so chosen are, with respect to traits governed entirely by this chromosome pair, composed of entirely unrelated individuals. But the fact that they are genetically unrelated, as far as the one chromosome pair is

concerned, cannot in any way cause them to be on the average *more different* from one another than unrelated individuals would be. If the latter appears to be the case, we must suspect that some unaccounted factor is at work. The rule, incidentally, still holds even if we select sib-pairs on the basis of multiple trait differences involving more than one chromosome pair. In fact, to give the extreme case, if it were possible for us to find a sib-pair in which not a single one of the parental stock of chromosomes occurred in both sibs, these two sibs would still have as much chance of being alike in any trait as would entirely unrelated individuals drawn from the same population.

Correction for Group Differences

When the aim of a study is to determine linkage, it is particularly essential that adequate correction be made for group differences between the sexes or between any other groups sorted for phenotype. A correlation within the population as a whole between two traits, if due to the pleiotropic action of a single gene on both traits in question, or to an influence of age, sex, or environment, on both traits, will yield positive results when linkage formulae are applied; so such a correlation must always be looked for and its effects discounted. The demonstration of linkage, as opposed to correlation otherwise caused, is based on the fact that linkage may produce correlation within sibships which is not evident in the population as a whole. In a typical linkage effect we would expect to find that, to give an example, in some families the taller individuals consistently had trait A while in other families the taller individuals consistently lacked trait A. This indicates that height is linked with trait A, but with greater height sometimes in a state of coupling with A and sometimes in a state of repulsion with it. If the coupling and repulsion effects cancel out, so as to leave no correlation between height and trait A in the population as a whole, we are assured that we are dealing with linkage and not with pleiotropism or the other factors mentioned above. It is possible that a general correlation may result from a strong linkage having preserved the trait combinations of anciently distinct racial groups in the population; this however we are not justified in assuming unless we can show that, independently of possible non-linkage correlations, there is also evidence of genetic linkage being present. Therefore if any population correlation exists between traits being tested for linkage it is necessary to estimate the amount of sib-pair variance which would be introduced by this factor and make due correction for it. Such a correction will be a blanket one, since it will allow for correlation due to pleiotropism, age, sex, environment or any combination of these factors.

Correction for group differences in the case of metric traits is not difficult, since it is strictly comparable to the calculation of a standard deviation where deviations are taken from an assumed mean which differs somewhat from the

true mean—an everyday occurrence in statistical work. In this familiar formula the correction factor (in our case equal to the absolute mean difference between groups, since zero is the assumed mean) is squared and subtracted from the mean squared deviation just before the extraction of the root which is the standard deviation. (The reader is referred to Appendix 1 for a short worked-out problem illustrating this correction.) This is an absolute algebraic correction and not an approximation, and gives the same result as if correction for the group difference were applied to individual measurements before the pair-comparisons were made. If the correction factor (the mean difference between the two groups compared) is less than one unit as compared with a true standard deviation of several units, the effect of the correction is surprisingly small.

TABLE 1. BODY BUILD, $\frac{\text{HEIGHT}}{\text{CUBE ROOT OF WEIGHT}}$

GROUP	MEAN ± STANDARD ERROR	STANDARD DEVIATION	NUMBER OF CASES
Total	12.78 ± .03	.57	298
Male	12.78 ± .05	.58	125
Female	12.77 ± .04	.56	173
Eye color Light	12.73 ± .06	.55	82
Eye color Intermediate	12.85 ± .06	.62	120
Iris structure Smooth (mixed or dark color)	12.73 ± .05	.51	96
Freckles absent	12.80 ± .04	.58	187
Freckles few	12.76 ± .07	.54	58
Freckles many	12.69 ± .08	.55	53

Corrections for group differences have been made except in the case of traits which were omitted from consideration after preliminary tests.[3] An examination of table 1 shows that when the population is sorted for sex, eye color and amount of freckling, no statistically significant group differences in body build appear. However, there are differences ranging up to one standard error in the case of eye color and freckling, and correction has been made for these differences. The corrections for these fractional differences are quite small, in the case of sex falling in the fourth decimal place and thus being discarded.

LINKAGE TESTS FOR BODY BUILD

Nine traits in all were tested for linkage with body build by determination of the standard deviations in body build of groups of sib-pairs selected for

[3] Theoretically a small group-difference correction should be made for the standard deviation of the *total* sib-pairs, in proportion to the group differences included in the whole series. But since the total is the statistical universe of the study, it has not been meddled with.

difference in the traits concerned. For convenience, sib-pairs alike in a given trait are called *S*-pairs, and sib-pairs differing in a given trait are called *D*-pairs. Table 2 gives the standard deviations in body build index of the *D*-pairs for each of the nine traits tested. In five cases the selected *D*-pairs show a greater degree of sib difference in body build than the total of all sib-pairs. However, the six traits in which the excess of sib difference in body build on the part of the *D*-pairs was negative or less than one standard error were dropped from further consideration, leaving only sex, eye color Light-versus-Intermediate, and freckling. In table 3 are given the statistical constants for both *S*-pairs and *D*-pairs for these three traits. It will be seen that so far the only statistically significant point (more than three times the standard error)

TABLE 2. BODY BUILD, $\frac{\text{HEIGHT}}{\text{CUBE ROOT OF WEIGHT}}$

SELECTION OF SIB-PAIRS	STANDARD DEVIATION OF SIB DIFFERENCES IN BODY BUILD ± STANDARD ERROR*	NUMBER OF CASES	DIRECTION AND SIGNIFICANCE OF DEVIATION FROM RANDOM
Total sib-pairs	.655	458	
Freckling different	.738 ± .036	209	+2.3
Eye color different, Light *versus* Intermediate	.777 ± .056	98	+2.2
Sex different	.702 ± .037	180	+1.3
Ear lobe, degree of attachment different	.675 ± .032	223	+0.6
Iris structure, scalloped *versus* cryptose	.663 ± .041	128	+0.2
Iris structure smooth *versus* non-smooth	.654 ± .046	103	0
Hair color different, in shade of brown	.642 ± .038	139	−0.3
Hair color different, red *versus* non-red	.642 ± .046	99	−0.3
Hair form different	.627 ± .028	242	−1.0

* All data in this table are as first derived without correction for group differences evident in the population.

is the less than average difference in body build in the case of sib-pairs alike in amount of freckling, and the difference between these *S*-pairs and their corresponding *D*-pairs.

The division of sib-pairs into *S*-pairs and *D*-pairs for any trait does not necessarily exhaust the analysis, since further subdivisions are possible which may give more significant differences if linkage is present. The first of these further subdivisions is that of the *D*-pairs into those showing a difference of one degree and those showing a difference of two degrees, where the trait is originally classified in three categories. Of the traits here considered two, sex and eye color Light-versus-Intermediate, have only two classes. In the case of freckling, the original data offer a multiple classification, so that the *D*-pairs may be divided into 1*D*-pairs, showing a difference as between few freckles and many or none, and 2*D*-pairs showing a maximum difference as

between no freckles and many. If, as is most certain, the observations as recorded do not correspond exactly to any set of genotypes, we cannot assume that 1*D* equals a one-gene difference and 2*D* a two-gene difference. But it can be assumed that 2*D* probably includes a higher percentage of two-gene differences than does the 1*D* class, and that it is relatively free of those cases in which the recorded difference is entirely due to minor modifiers or non-genetic causes.

TABLE 3. BODY BUILD, $\frac{\text{HEIGHT}}{\text{CUBE ROOT OF WEIGHT}}$

SELECTION OF SIB-PAIRS	STANDARD DEVIATION OF SIB DIFFERENCES IN BODY BUILD ± STANDARD ERROR	NUMBER OF CASES	DIRECTION AND SIGNIFICANCE OF DEVIATION FROM RANDOM
Total sib-pairs	.655	458	
Sex same, sisters	.636 ± .032	191	−0.6
Sex same, brothers	.581 ± .044	87	−1.7
All sex same	.616 ± .026	278	−1.5
Sex different*	.702 ± .037	180	+1.3
Difference between above two classes	.086 ± .045		1.9
Freckling same	.572 ± .026	249	−4.5
Freckling different*	.735 ± .036	209	+2.3
Difference between above two classes	.163 ± .044		3.7
Eye, Light versus Intermediate			
Same	.635 ± .034	169	−0.6
Different*	.765 ± .055	98	+2.3
Difference between above two classes	.130 ± .065		2.0

* Corrected for group differences evident in the population.

In freckling, the 2*D*-pairs show a considerably higher degree of difference in body build than do the *D*-pairs as a whole (table 4). However, the much smaller numbers decrease the significance of the difference though the difference itself is increased.

The second route of further analysis lies in selection of sibships. The *S*-pairs drawn from the total series will inevitably include a considerable number of sib-pairs from families which were in fact relatively homozygous for the trait in question. Such families are of course useless for purposes of determining linkage, since the various chromosomes current in them cannot be distinguished from one another by reference to this particular trait. Similarity between two siblings in a trait does not become significant for purposes of determining linkage until it is known that a variety of determining genes is present in the family. Thus, if a selection of sibships is made, the *S*-pairs

in demonstrably heterozygous sibships will represent a group more highly selected for chromosomal similarity than are all *S*-pairs in general. We will sometimes make the mistake of eliminating, as apparently homozygous, sibships which might have shown a variety of phenotype if more members had been observed; this cannot be helped. Sibships of two sibs only were eliminated from this part of the analysis; all others are included in table 4. However, it is still possible to draw a considerable number of *S*-pairs from demonstrably heterozygous sibships, so that we may make the critical comparison between *S*-pairs and *D*-pairs within the sibships in which *D*-pairs occur.

TABLE 4. BODY BUILD, $\frac{\text{HEIGHT}}{\text{CUBE ROOT OF WEIGHT}}$

SELECTION OF SIB-PAIRS	STANDARD DEVIATION OF SIB DIFFERENCES IN BODY BUILD ± STANDARD ERROR	NUMBER OF CASES	DIRECTION AND SIGNIFICANCE OF DEVIATION FROM RANDOM
Total sib-pairs	.655	458	
Freckling different by two degrees*	.765 ± .064	71	+1.7
Freckling same, heterozygous families	.509 ± .030	149	−4.9
Freckling same, homozygous families	.654 ± .046	100	0
Eye color, Light versus Intermediate:			
Same, heterozygous families	.638 ± .045	103	−0.4
Same, homozygous families	.622 ± .054	66	−0.6

* Corrected for group differences evident in the population.

In the case of sex, no such selection should be made, since all families are heterozygous for sex even if the issue does not show it. The results for eye color and freckling are given in table 4. The results in respect to eye color are negative. In the case of freckling, however, the *S*-pairs from heterozygous sibships show a similarity in body build considerably greater even than that for all *S*-pairs. The remainder—*S*-pairs from sibships not visibly heterozygous —are indistinguishable from the total of the series. This is to be expected, since in truly homozygous families the "S" classification means nothing for purposes of linkage, and *S*-pairs from such families would be actually unselected for chromosome likeness. This clear distinction between *S*-pairs from demonstrably heterozygous sibships and other *S*-pairs finally disposes of any suspicion that the increased similarity in body build between siblings alike in freckling could be due to any form of correlation other than genetic linkage.

If all three of the traits under consideration are in fact linked to body build, we may expect that sib-pairs in which the two sibs differ in respect to more than one trait will show greater divergence in body build than those in

which one trait only differs. This may result from any of several causes. If more than one chromosome pair is involved, the multiple selection may be giving us four or even six-chromosome sortings which result in clearer body build differentiation. However, multiple sorting will give positive results even if the linkages are all in one chromosome pair. A difference in more than one trait is more likely to represent a real chromosomal difference, rather than a

TABLE 5. BODY BUILD, $\frac{\text{HEIGHT}}{\text{CUBE ROOT OF WEIGHT}}$

SELECTION OF SIB-PAIRS	STANDARD DEVIATION OF SIB DIFFERENCES IN BODY BUILD ± STANDARD ERROR	NUMBER OF CASES	DIRECTION AND SIGNIFICANCE OF DEVIATION FROM RANDOM
Total sib-pairs	.655	458	
Freckling and sex:			
Same, both traits	.547 ± .031	153	−3.5
Different, both traits*	.790 ± .061	84	+2.2
Difference between above two classes	.243 ± .069		3.5
Freckling and eye color, Light versus Intermediate:			
Same, both traits	.504 ± .037	91	−4.1
Different, both traits*	.826 ± .087	45	+2.0
Difference between above two classes	.322 ± .095		3.4
Sex and eye color, Light versus Intermediate:			
Same, both traits	.606 ± .043	99	−1.1
Different, both traits*	.824 ± .082	50	+2.1
Difference between above two classes	.218 ± .093		2.3
Freckling, sex, and eye color:			
Same, all three traits	.496 ± .047	56	−3.4
Different, all three traits*	.940 ± .142	22	+2.0
Difference between above two classes	.444 ± .149		3.0
Difference between pairs of unrelated individuals	.804		

* Corrected for group differences evident in the population.

difference in a modifier or a misjudgement of observation. In this sense one trait is merely a check on the other. A two-trait difference is also more likely to represent a difference in both chromosomes of the pair. And finally, if crossing-over is frequent (a possibility we have so far disregarded) a multiple-trait difference is more likely to be indicative of a difference involving a whole chromosome.

An examination of table 5 shows that all combinations of the three traits, freckling, eye color and sex, give differentiation of sib-pair groups more marked

than were obtained by the single traits. In fact, disconcertingly enough, in three cases (freckling and eye color, sex and eye color, and all three traits together) a sorting for multiple differences between sibs brings into being sib-pair groups in which the divergence in body build is *more* than that randomly expected of unrelated individuals, in spite of correction for mean group differences in the population. As explained earlier in this paper, linkage alone could not produce such a result. Fortunately in these more highly selected and smaller groups the standard errors are sufficiently large to explain away the anomalous result.

There are two ways in which we may compare the result of our various linkage sortings: by absolute differences and by statistical significance. Since our various sortings give groups of extremely different size and statistical reliability, the perspective is altered by the method of comparison. In the first case we are comparing the most probable true values; in the second case considering the probability that the apparent differences between them are real.

On the basis of the mean or most probable true values, freckling is the outstanding trait in body build linkage as judged by the difference between its *S*-pairs and *D*-pairs. Eye color Light-*versus*-Intermediate comes second, sex last. On the basis of *D*-pairs alone, eye color rates highest. But its *S*-pairs are not very different from the total series.[4] In the sortings for two traits the combination of freckling and eye color gives the greatest contrast of *S*-pairs and *D*-pairs. Freckling and sex combined rate second, sex and eye color combined the lowest. The combination of all three gives the most marked differentiation of *S*-pairs and *D*-pairs. In general, the multiple sortings give differences in line with the magnitude of effect of their various components.

On the basis of statistical significance, none of the sortings except those involving freckling are completely convincing; the increased differentiation due to multiple sorting is cancelled out by the increase in standard error due to the smaller size of the groups. Consequently we cannot state as positive statistical fact any linkage of body build except that with freckling, although we may consider it extremely likely that sex and eye color are involved also (99 percent probability on the basis of 2.3 standard error derived from a double sorting; cf. table 5).

The question now arises of the linkage of these three traits with one another. Sex and eye color (Light *versus* Intermediate) have already been shown to

[4] This discrepancy is explained by the fact that two-fifths of our total sib-pairs are not classifiable in regard to Light-*versus*-Intermediate because they involve one or two dark-eyed individuals. The pairs thus eliminated have a low variance, not suggestive of linkage but of a general stability of body build in the dark-eyed individuals of the series. This footnote is a small explanation for a curious matter.

be linked (Brues, 1946). A check of these two traits against freckling, both separately and together, gives no evidence of linkage with freckling. Out of

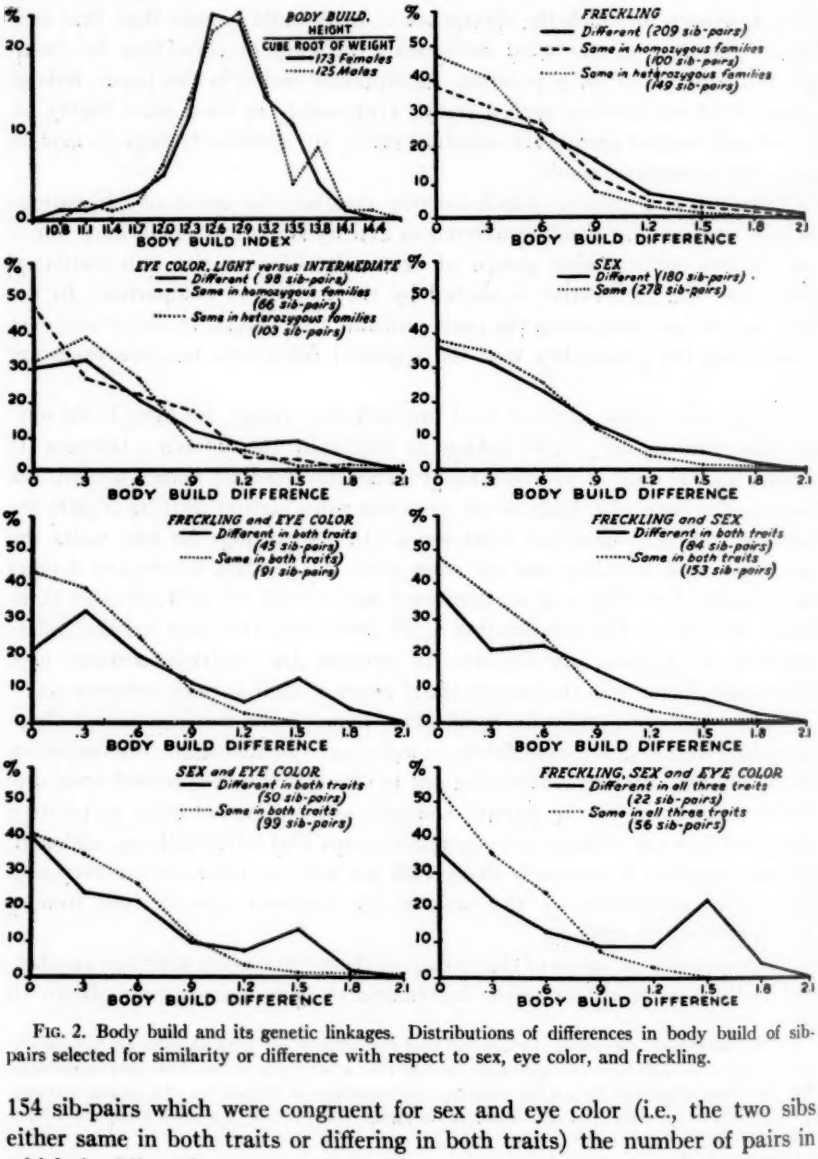
BODY BUILD, HEIGHT / CUBE ROOT OF WEIGHT
173 Females
125 Males
BODY BUILD INDEX
FRECKLING
Different (209 sib-pairs)
Same in homozygous families (100 sib-pairs)
Same in heterozygous families (149 sib-pairs)
BODY BUILD DIFFERENCE
EYE COLOR, LIGHT versus INTERMEDIATE
Different (98 sib-pairs)
Same in homozygous families (66 sib-pairs)
Same in heterozygous families (103 sib-pairs)
BODY BUILD DIFFERENCE
SEX
Different (180 sib-pairs)
Same (278 sib-pairs)
BODY BUILD DIFFERENCE
FRECKLING and EYE COLOR
Different in both traits (45 sib-pairs)
Same in both traits (91 sib-pairs)
BODY BUILD DIFFERENCE
FRECKLING and SEX
Different in both traits (84 sib-pairs)
Same in both traits (153 sib-pairs)
BODY BUILD DIFFERENCE
SEX and EYE COLOR
Different in both traits (50 sib-pairs)
Same in both traits (99 sib-pairs)
BODY BUILD DIFFERENCE
FRECKLING, SEX and EYE COLOR
Different in all three traits (22 sib-pairs)
Same in all three traits (56 sib-pairs)
BODY BUILD DIFFERENCE

FIG. 2. Body build and its genetic linkages. Distributions of differences in body build of sib-pairs selected for similarity or difference with respect to sex, eye color, and freckling.

154 sib-pairs which were congruent for sex and eye color (i.e., the two sibs either same in both traits or differing in both traits) the number of pairs in which freckling also concurred was 81 as compared with a random expecta-

tion of 79.4. So we probably have two major body build factors, one sex-linked and the other linked with freckling in another chromosome. Less likely is the possibility that the entire complex is in the sex chromosome with a high rate of crossing-over between freckling and the sex-eye color segment, and one body build factor somewhere between.

The question of whether one or two factors are involved may be enlightened by the percentage distributions.[5] These show not only the degrees of divergence of various selected groups of sib-pairs, but the absolute amounts of sib-difference which are in excess in the various groups. Examination of these graphs (fig. 2) shows that difference in freckling correlates with an excess of body build differences ranging from 0.8 on up, whereas difference in sex or eye color or both correlates with a peak of differences at 1.5. The series is not large enough to prove in this way that two separate factors of different magnitude are acting, but it appears likely. Combined differences in both freckling and the sex chromosome show an only partially additive effect in magnitude of difference, since the virtual limit of sib differences in body build is at 2.0. Multiple sorting appears to act by increasing the likelihood of a difference being present more than by increasing the magnitude of the difference. Since a body build index difference of 2.0 represents a weight difference of nearly 50% for the same height, it is not surprising that the law of diminishing returns takes effect.

CONCLUSIONS

Apparently we have isolated two important factors influencing body build, one located in the sex chromosome and one in the chromosome that contains an important freckle determiner. Since the preliminary sortings show no linkage of body build with red hair, any pleiotropic factor involving freckling and hair color must be elsewhere. A difference between two sibs in regard to the sex-linked determiner is likely to be correlated with a body build difference of about 1.5 units. A difference between two sibs in regard to the freckle-linked determiner is likely to be correlated with a more moderate and variable body build difference of 0.8 or more. The freckle-linked difference, though not as great in individual cases, is more striking statistically because it appears more consistently, probably due to the fact that the alternate body build genes involved are in more nearly 50-50 ratio in the population.

A phenotypic selection on the basis of linked traits shows that a difference

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[5] In plotting these distributions the zero class is multiplied by two to bring it into proper proportion to the other classes which represent plus and minus values of the same amount combined. Without this adjustment the curve always presents an anomalous drop at the zero point.

between sibs in respect to both of these factors is sufficient to upset the genetic balance to the extent of erasing family resemblance in body build altogether. A double-checked sex-chromosome difference (i.e., both sex and eye color different) appears to do the same, but with a smaller margin of statistical significance. It is impossible to say with certainty, because of the standard errors of the groups, to what extent the effects of the factor differences are additive. It is probable, however, that a difference in a single factor disrupts the genetic balance more than would be indicated by a scheme of simple addition of effect. Certainly there is no reason to suppose that a likeness in respect to both of the factors we have isolated must be sufficient to establish body build likeness beyond the power of any other factor to upset it. We can only say that in the present population the other factors which may be involved are either not comparable in effect to the two principal ones or are not frequent in occurrence. This may be seen in the graphic representation of the pairs selected for likeness in all three traits. This group is of course not a pure one, since phenotypic likeness does not guarantee chromosome likeness. Normally only one-sixteenth of all sib-pairs would be alike in respect to all four chromosomes of two chromosome pairs; our selected group is nearly twice that size. But it nevertheless shows a remarkable lack of pronounced body build differences.

Once linkage is demonstrated, the probability arises that the general slight association in the population of Light eyes and freckling with heavier body build is a remote effect of racial mixture, which has persisted because of the linkage. If this is the case, then our corrections for group differences have been wrongly applied, as the group differences are legitimately due to linkage and not to any other form of influence. Whether or not this is true can hardly be certainly proved one way or the other. The group differences within the population are within the range of sampling error in any case.

In retrospect, several points of interest appear in the investigation aside from the specific allocation of factors to chromosomes. An important consideration in any study of body build is the extent to which weight is self-regulating, difference in choice of diet being consequent on body build and not vice versa. The problem of weight change with advancing age is a part of the same question, since age changes, if not predestined, represent cumulative effects of non-genetic influence. The determination of heredity of build is complicated by the possibility of dietary habits being transmitted sociologically so that build might thus be familial without being truly hereditary. The demonstration that differences in body build within the family are genetically linked to other traits effectively rules out sociological inheritance, cytoplasmic inheritance and casually acquired food habits as effective determiners of build, and indicates that weight regulation comes strictly under control of

the genes, the extrinsic factors being under ordinary circumstances relegated to the position of modifiers.

Body build is apparently basically controlled by far fewer genes than might *a priori* have been expected. The fewness of major determiners provokes speculation in view of the highly polygenic determination of size shown in some experimental work. It may be possible that the complexity of development in a mammal favors the elevation of a few genes to key position, in contrast to the amorphous interchangeability of many size determiners which has been found particularly in plants. Perhaps also we must admit beginner's luck in having hit on a conventional morphological index which happens to correspond closely to a simple developmental reality. The linkage, in fact, affords an interesting test of the genetic relevance of a particular scale of measurement, and offers a means of determining the relative validity of dimensions and indices.

Of special interest to the anthropologist is the fact that good linkages have been obtained by the use of a subjective judgement of freckling, a type of observation which one tends to regard with suspicion for purposes of exact analysis. Anyone who has made observations of this sort will admit that often a given observation, repeated, might not be recorded the same. But such observations are so necessary to complete the picture of anthropological variation that traits subject only to this kind of rating cannot, and need not, be left untouched because of a feeling of guilt regarding the incomplete precision of the measurement.

Most encouraging for anthropology, however, is the cracking of the normal curve, which has always confronted the anthropologist seeking genetic understanding with the specter of "many small, equal, independent factors." But this barrier now seems more apparent than real, needing only to be approached with weapons slightly more substantial than speeches advocating the coordination of genetics and anthropology.

Some interest attaches to the number of things which have *not* been determined in this study. If each separate investigation were to recapitulate the history of genetics in general, it would be necessary first to determine the units of inheritance of each trait, the relation of phenotype to genotype, and the presence or absence of dominance, before attempting to demonstrate linkage. If this procedure had been followed in the case of freckling and body build, the whole study would have bogged down in the first stage. The determination of "units" in morphological traits has always been a mire to which most investigators have not returned a second time. However, if linkages can be proved, the units cannot remain concealed. Linkage, in spite of its late appearance in the history of genetics, is apparently in man the easiest thing of all to demonstrate, and makes a good starting point for genetic studies.

TABLE 6. ORIGINAL DATA

Key: No. = series number; the digit indicates the family, the letter the individual. H = height in centimeters. BBI = body build index (height in inches divided by cube root of weight in pounds). E-Str = iris structure: *Sm* = smooth, *Sc* = scalloped, *Cr* = cryptose. E-C = eye color: *L* = Light. *I* = Intermediate. FR = freckles: *A* = absent, *Sm* = few, + = many. HC-B = hair color—*brown*: *D* = dark brown, *M* = medium brown, *L* = light brown or fair. HC-R = hair color—*red*; *R* = red, *O* = non-red. HF = hair form: *S* = straight, *L* = low wave, *D* = deep wave or curly. EL = degree of attachment of ear lobe: *F* = free, *A* = attached, *S* = soldered.

No.	Sex	Age	H	BBI	E-Str	E-C	FR	HC-B	HC-R	HF	EL
1-A	F	28	154	12.8	Sm	—	Sm	D	—	S	A
1-B	M	24	163	12.4	Sc	I	+	D	—	S	A
1-C	F	20	159	13.5	Sc	I	+	L	R	S	A
2-A	F	28	164	12.5	Cr	I	+	D	—	L	F
2-B	F	22	160	12.7	Sc	I	Sm	M	O	S	A
2-C	M	19	180	12.8	Cr	I	Sm	M	R	S	F
2-D	M	25	180	13.3	Cr	I	A	D	—	S	F
3-A	F	26	170	12.6	Sc	I	A	M	O	L	A
3-B	F	32	162	12.1	Sc	L	Sm	M	O	L	A
3-C	F	31	162	12.7	Sc	I	A	D	—	L	A
3-D	F	29	162	12.3	Cr	L	A	M	O	S	A
3-E	F	37	160	12.6	Cr	L	A	D	—	L	A
3-F	M	24	181	12.7	Cr	L	A	D	—	L	A
3-G	M	22	180	12.8	Cr	L	A	M	O	L	F
4-A	M	25	176	13.3	Sm	—	A	D	—	S	S
4-B	F	21	155	13.1	Sc	I	A	D	—	S	A
5-A	F	22	173	13.2	Sc	L	A	L	O	S	S
5-B	M	21	177	12.7	Cr	I	A	D	—	S	A
5-C	M	19	189	13.0	Sc	L	A	M	O	L	S
6-A	M	20	182	12.8	Cr	I	A	D	—	L	F
6-B	F	25	166	12.6	Cr	I	A	D	—	S	A
6-C	F	22	174	13.1	Sc	I	+	D	—	S	A
6-D	M	28	190	12.6	Sc	L	A	D	—	S	F
7-A	M	27	181	13.4	Sm	—	A	D	—	D	A
7-B	M	22	186	12.9	Sm	—	A	D	—	D	A
8-A	M	32	172	11.6	Cr	I	Sm	M	O	S	F
8-B	M	35	165	11.8	Sc	I	+	D	—	S	F
9-A	M	21	192	13.7	Cr	I	Sm	L	R	S	F
9-B	M	18	192	14.2	Cr	I	Sm	M	R	S	F
9-C	M	22	184	13.3	Cr	I	A	M	O	L	F
9-D	F	18	179	14.2	Sc	I	A	M	R	S	S
10-A	F	20	164	12.2	Sm	—	Sm	D	—	L	A
10-B	F	22	165	12.2	Sm	—	Sm	D	—	L	S
10-C	M	18	178	13.0	Sm	—	A	D	—	L	F
11-A	F	22	165	12.6	Sm	—	Sm	L	O	L	A
11-B	F	24	162	12.6	Sm	—	Sm	D	—	S	F
11-C	F	28	168	13.3	Sm	—	A	M	O	L	F
12-A	F	20	160	13.2	Cr	I	+	L	R	L	A
12-B	F	18	171	13.0	Cr	I	Sm	L	O	D	A
12-C	M	24	178	13.1	Cr	I	A	L	O	S	F
12-D	F	23	164	12.5	Sc	I	Sm	L	O	L	F

TABLE 6.—*Continued*

No.	Sex	Age	H	BBI	E-Str	E-C	FR	HC-B	HC-R	HF	EL
13-A	F	26	162	13.0	Cr	I	Sm	M	R	S	A
13-B	F	22	163	12.7	Cr	I	Sm	D	—	S	F
13-C	M	24	169	12.3	Sc	L	Sm	M	O	S	F
13-D	F	33	160	12.6	Sc	L	+	M	O	S	A
13-E	F	37	156	10.8	Cr	I	A	D	—	S	F
13-F	M	37	166	11.1	Sc	I	A	D	—	S	A
13-G	F	30	154	12.4	Cr	L	A	D	—	L	A
14-A	F	27	165	13.1	Sc	L	Sm	L	O	L	F
14-B	F	21	158	12.8	Sc	L	+	M	O	D	A
14-C	F	26	164	12.6	Sc	L	Sm	L	O	L	F
14-D	F	29	164	12.9	Sc	L	Sm	L	O	L	F
14-E	F	24	172	13.4	Sc	I	A	L	O	S	A
15-A	F	26	156	12.4	Sm	—	+	D	—	S	A
15-B	F	31	154	11.9	Sm	—	A	D	—	L	A
15-C	M	28	162	12.3	Sc	I	A	M	R	D	F
16-A	F	20	167	13.3	Cr	I	Sm	M	O	S	F
16-B	M	30	186	13.0	Cr	L	A	D	—	L	A
16-C	F	23	164	13.4	Sm	—	A	D	—	S	A
17-A	F	52	155	11.0	Cr	I	Sm	D	—	S	A
17-B	F	37	155	11.3	Cr	I	Sm	M	O	S	F
17-C	M	42	169	12.5	Cr	L	A	L	O	S	F
17-D	M	40	169	12.9	Sc	L	A	M	O	S	A
17-E	M	46	164	12.6	Cr	L	A	D	—	S	F
18-A	M	38	168	12.7	Sc	L	A	L	O	S	S
18-B	F	32	165	12.3	Sm	—	A	D	—	S	A
19-A	M	26	179	12.9	Sc	I	A	M	O	S	S
19-B	M	19	174	12.3	Cr	I	A	D	—	S	A
19-C	M	18	182	11.1	Sc	L	A	D	—	L	F
20-A	F	23	169	13.5	Sm	—	A	D	—	S	S
20-B	M	28	188	12.8	Sc	I	A	D	—	L	A
21-A	M	22	173	12.5	Cr	I	A	D	—	D	F
21-B	M	21	173	13.1	Cr	I	+	M	O	D	F
22-A	F	27	155	12.4	Sm	—	A	D	—	S	A
22-B	F	20	159	12.9	Sm	—	A	M	O	S	A
22-C	M	25	169	12.5	Sm	—	A	D	—	L	S
22-D	F	24	161	12.7	Sm	—	A	D	—	S	F
22-E	F	22	158	12.0	Sm	—	A	M	R	D	A
23-A	F	26	161	13.1	Sm	—	Sm	D	—	D	A
23-B	F	30	166	13.7	Cr	I	A	D	—	L	F
23-C	F	22	169	13.0	Sm	—	+	D	—	L	F
24-A	M	29	177	13.1	Sc	L	A	L	O	L	F
24-B	M	35	174	12.8	Sc	I	Sm	D	—	D	F
24-C	F	38	168	13.6	Cr	I	A	D	—	S	F
24-D	F	24	166	12.9	Cr	L	A	M	R	D	F
24-E	F	37	164	13.2	Cr	I	A	D	—	L	F
24-F	M	31	182	13.4	Cr	L	A	M	O	S	A
24-G	F	33	170	13.7	Cr	I	A	D	—	D	F
24-H	F	27	171	13.7	Cr	I	Sm	D	—	S	S

TABLE 6.—*Continued*

No.	Sex	Age	H	BBI	E-Str.	E-C	FR	HC-B	HC-R	HF	EL
25-A	M	27	177	12.8	Sc	L	A	M	O	L	A
25-B	M	28	172	12.4	Sc	L	A	D	—	L	F
25-C	F	25	162	12.8	Cr	L	A	L	R	L	A
25-D	F	31	163	11.6	Sc	I	A	M	O	S	A
25-E	F	23	158	12.7	Sm	—	Sm	D	—	L	A
26-A	F	27	156	12.0	Sm	—	A	D	—	S	A
26-B	F	24	153	12.7	Sm	—	A	M	O	S	S
26-C	M	23	176	13.0	Sm	—	A	M	O	L	A
27-A	F	23	166	12.1	Sc	L	A	M	O	S	F
27-B	F	18	158	12.5	Sm	—	A	D	—	S	F
27-C	F	20	163	13.1	Cr	I	A	D	—	S	A
27-D	M	22	177	12.6	Cr	I	A	D	—	S	A
28-A	F	27	151	12.9	Cr	I	A	L	O	S	F
28-B	M	24	166	12.8	Sm	—	A	L	O	S	F
29-A	F	31	172	13.1	Sm	—	A	L	O	S	F
29-B	F	35	173	12.4	Sm	—	A	D	—	S	F
29-C	M	23	195	14.3	Cr	L	A	D	—	S	F
29-D	F	29	174	13.4	Sc	I	A	D	—	S	F
30-A	F	26	155	13.0	Sc	L	A	L	O	S	A
30-B	F	41	156	12.4	Sc	L	A	M	O	L	A
30-C	F	38	159	12.5	Cr	I	A	L	O	D	F
30-D	F	33	160	12.8	Sc	L	A	D	—	S	F
31-A	F	31	157	12.9	Sm	—	+	D	—	S	F
31-B	F	21	160	13.2	Sm	—	A	D	—	D	A
31-C	F	26	161	12.9	Sm	—	+	M	R	L	A
31-D	F	20	157	13.6	Sm	—	+	D	—	L	F
31-E	F	32	152	12.5	Sc	I	A	D	—	D	A
31-F	F	26	168	13.7	Cr	I	A	D	—	S	F
31-G	F	30	162	13.7	Sm	—	Sm	D	—	S	F
32-A	F	25	166	12.8	Sm	—	A	D	—	L	F
32-B	F	21	163	12.7	Sc	I	+	M	R	S	F
33-A	M	24	180	13.3	Sc	I	A	L	O	S	F
33-B	M	33	183	13.7	Sc	L	A	L	O	S	F
33-C	M	38	185	13.7	Cr	L	A	M	O	S	F
34-A	F	23	156	12.7	Cr	L	+	D	—	S	F
34-B	F	33	155	12.1	Sc	L	+	D	—	S	A
34-C	F	28	150	13.0	Sc	I	+	D	—	L	F
34-D	F	26	157	13.3	Sc	L	Sm	M	O	S	F
35-A	F	34	172	12.9	Sm	—	A	D	—	S	A
35-B	F	21	164	13.4	Cr	I	A	M	R	S	F
35-C	M	23	183	13.7	Sc	I	A	D	—	S	F
35-D	M	32	181	13.6	Sc	I	A	D	—	L	F
35-E	F	18	168	13.5	Sc	I	A	D	—	L	F
36-A	F	27	170	13.4	Sc	L	A	L	O	L	F
36-B	M	24	177	13.9	Sc	L	A	L	O	D	A
37-A	F	18	162	12.9	Cr	I	A	D	—	L	F
37-B	M	32	180	13.5	Cr	I	A	D	—	S	F
37-C	F	28	158	12.8	Sc	I	A	L	O	S	F
37-D	M	31	165	13.0	Cr	I	A	D	—	L	F

TABLE 6.—*Continued*

No.	Sex	Age	H	BBI	E-Str.	E-C	FR	HC-B	HC-R	HF	EL
38-A	F	57	170	12.6	Sm	—	A	M	R	L	F
38-B	F	67	165	12.5	Sm	—	A	D	—	D	F
38-C	F	57	169	12.8	Sm	—	Sm	M	R	S	F
38-D	F	55	171	12.3	Sm	—	A	D	—	L	F
39-A	M	30	173	12.1	Cr	I	A	D	—	S	F
38-B	F	22	163	13.6	Sm	—	A	D	—	S	F
39-C	M	25	174	13.2	Sm	—	A	D	—	S	F
40-A	M	37	176	12.8	Sm	—	A	D	—	L	F
40-B	M	34	173	13.0	Sc	I	A	M	O	S	A
40-C	M	40	164	12.9	Sm	—	A	D	—	S	F
40-D	M	44	171	13.0	Sm	—	A	M	R	D	A
40-E	M	46	170	12.7	Sm	—	A	D	—	S	S
41-A	M	60	177	12.2	Cr	L	A	L	O	D	F
41-B	F	57	158	12.8	Sm	—	+	D	—	D	F
41-C	M	52	180	12.4	Cr	I	+	D	—	S	A
41-D	F	64	155	11.8	Sc	I	A	D	—	S	F
42-A	F	24	158	12.8	Sc	I	A	M	O	S	F
42-B	F	19	157	12.4	Cr	I	Sm	M	R	S	S
42-C	F	32	165	13.8	Sc	I	A	L	O	S	A
42-D	F	26	160	12.9	Sc	I	A	L	O	S	F
43-A	F	29	168	13.6	Sm	—	Sm	D	—	S	A
43-B	M	31	174	12.6	Cr	L	A	D	—	S	A
44-A	M	65	174	12.2	Sc	L	A	M	O	S	A
44-B	M	49	172	12.7	Sc	L	A	M	O	—	F
45-A	M	25	178	12.9	Sc	L	A	D	—	S	F
45-B	F	21	167	12.4	Sm	—	A	D	—	S	A
45-C	M	23	181	12.6	Sc	I	A	D	—	S	F
46-A	M	33	180	12.2	Cr	L	A	D	—	D	F
46-B	M	21	184	13.3	Sm	—	A	D	—	S	F
46-C	M	25	178	12.0	Sc	L	A	M	O	D	F
47-A	F	30	170	13.2	Sm	—	A	L	O	L	S
47-B	F	24	172	13.0	Sm	—	A	L	O	L	F
47-C	F	33	171	12.3	Sm	—	A	L	R	S	A
47-D	F	26	173	13.1	Sc	I	A	L	O	L	S
48-A	F	48	169	12.4	Sc	L	A	D	—	L	F
48-B	F	32	170	13.0	Sm	—	A	D	—	S	F
48-C	F	29	168	13.2	Cr	I	Sm	D	—	L	F
48-D	F	44	161	12.0	Cr	I	Sm	D	—	S	A
48-E	M	39	182	12.5	Sm	—	+	D	—	S	F
49-A	M	32	179	12.4	Sc	L	A	D	—	D	F
49-B	F	22	166	12.7	Sc	I	+	M	R	D	F
49-C	M	28	182	12.2	Sc	I	+	D	—	S	F
50-A	F	21	166	13.0	Sc	I	A	M	O	S	F
50-B	F	32	164	12.8	Sc	I	A	M	O	S	F
51-A	M	41	177	12.4	Sc	L	Sm	L	O	S	F
51-B	M	36	192	12.9	Cr	L	A	L	O	S	F
51-C	F	24	170	13.2	Cr	I	A	L	O	D	F
51-D	F	38	166	—	Sc	I	+	M	R	L	A
51-E	F	28	168	12.8	Sm	—	Sm	L	O	L	F
51-F	M	41	181	13.3	Sc	L	Sm	M	O	S	F

TABLE 6.—*Continued*

No	Sex	Age	H	BBI	E-Str.	E-C	FR	HC-B	HC-R	HF	EL
52-A	M	22	171	12.6	Cr	L	A	L	O	L	F
52-B	M	19	164	12.8	Sc	L	A	L	O	S	F
53-A	F	33	179	12.7	Cr	L	+	M	O	L	A
53-B	M	31	179	12.6	Cr	I	A	M	R	S	A
53-C	F	35	169	13.0	Sc	L	+	M	O	S	A
54-A	F	26	166	12.9	Sc	L	+	D	—	L	F
54-B	M	24	179	12.7	Sc	L	A	L	O	S	S
55-A	M	25	183	13.3	Sc	I	+	L	O	S	S
55-B	F	21	165	12.8	Sc	I	+	L	O	D	F
55-C	F	22	159	12.7	Sc	I	Sm	D	—	S	A
55-D	M	18	185	13.1	Cr	L	+	M	O	L	S
56-A	F	35	175	12.9	Sc	I	Sm	D	—	S	A
56-B	F	31	169	13.3	Cr	I	+	D	—	L	F
56-C	M	28	184	12.1	Sc	I	A	M	O	C	F
57-A	M	30	178	13.5	Cr	I	A	D	—	S	F
57-B	F	34	160	12.6	Sc	I	A	D	—	L	F
57-C	F	25	156	13.3	Sc	L	A	D	—	D	A
57-D	M	33	173	12.0	Sc	L	+	D	—	L	F
58-A	F	57	151	11.3	Sc	I	+	D	—	L	A
58-B	M	61	164	12.4	Cr	I	A	D	—	S	F
58-C	M	53	152	11.7	Sm	—	A	D	—	S	S
59-A	F	20	159	13.4	Sm	—	+	L	O	L	F
59-B	F	29	157	12.6	Cr	I	A	L	O	L	F
59-C	F	28	154	12.5	Sc	I	A	L	O	D	F
59-D	F	25	160	13.1	Sm	—	A	L	O	D	F
60-A	M	25	164	13.1	Sm	—	A	M	O	S	F
60-B	M	27	173	13.3	Sm	—	A	M	O	S	F
61-A	F	33	168	13.3	Cr	I	Sm	L	R	S	F
61-B	M	38	187	13.1	Sc	I	A	D	—	S	F
61-C	F	30	173	13.0	Sc	I	Sm	D	—	S	F
62-A	F	27	167	12.7	Sm	—	+	D	—	S	F
62-B	F	33	172	12.4	Sc	L	+	D	—	S	F
62-C	F	36	166	12.5	Sc	L	+	D	—	L	A
63-A	M	31	165	12.7	Sm	—	A	D	—	L	F
63-B	M	24	181	13.0	Sm	—	A	D	—	S	F
63-C	F	18	155	12.9	Sm	—	A	D	—	L	F
63-D	M	36	173	13.0	Sm	—	A	D	—	S	F
63-E	M	34	172	12.5	Sm	—	A	D	—	L	A
63-F	F	27	166	13.5	Sm	—	+	D	—	D	F
64-A	M	38	174	12.2	Cr	I	A	M	R	L	F
64-B	F	44	162	12.5	Cr	I	A	M	O	S	F
64-C	M	50	173	11.9	Sm	—	+	D	—	S	S
64-D	F	49	157	12.1	Sm	—	+	D	—	S	F
64-E	F	32	161	12.5	Sc	I	Sm	M	R	S	S
64-F	F	34	172	12.5	Sm	—	Sm	D	—	D	S
65-A	F	26	158	12.4	Sc	L	+	M	R	L	A
65-B	M	21	175	13.8	Sc	L	A	D	—	S	F
65-C	F	24	162	12.8	Sc	L	Sm	D	—	L	F
65-D	M	19	179	13.7	Sc	L	A	D	—	S	F

TABLE 6.—*Continued*

No.	Sex	Age	H	BBI	E-Str.	E-C	FR	HC-B	HC-R	HF	EL
66-A	M	35	—	—	Sc	L	A	L	O	S	A
66-B	M	32	167	12.8	Sc	I	A	M	O	S	F
66-C	M	43	172	12.1	Cr	I	A	D	—	L	A
66-D	F	40	154	11.8	Sc	I	A	M	R	S	A
67-A	F	30	155	12.5	Sc	I	+	L	O	S	F
67-B	F	22	165	13.4	Sm	—	Sm	D	—	S	A
67-C	F	24	165	13.4	Sm	—	A	D	—	D	S
68-A	M	35	171	12.7	Cr	I	A	M	O	S	A
68-B	F	25	157	12.8	Sc	I	Sm	D	—	L	A
68-C	F	32	161	12.2	Cr	I	Sm	D	—	S	A
69-A	M	27	172	12.5	Cr	I	Sm	L	O	S	F
69-B	M	20	165	13.0	Sc	I	A	M	O	S	F
69-C	M	24	164	12.6	Sc	L	Sm	L	O	S	F
70-A	F	22	166	12.3	Cr	L	A	D	—	D	A
70-B	F	18	172	13.1	Sc	L	A	M	R	S	F
70-C	M	25	182	13.1	Sc	I	A	D	—	L	A
70-D	M	26	183	13.7	Cr	I	A	D	—	L	S
70-E	M	19	188	13.8	Cr	I	A	D	—	S	F
71-A	F	17	170	12.4	Sm	—	+	M	O	S	A
71-B	F	19	179	11.9	Sm	—	+	L	R	S	A
71-C	F	23	170	13.4	Sc	I	A	L	O	D	S
72-A	F	24	159	12.4	Sm	—	Sm	D	—	S	F
72-B	F	22	161	12.3	Sm	—	A	D	—	D	F
73-A	F	21	161	13.8	Sc	I	+	M	O	S	F
73-B	F	23	162	13.5	Sc	I	+	L	O	S	F
73-C	F	28	156	12.6	Sc	I	Sm	D	—	S	F
73-D	F	26	150	12.9	Cr	I	Sm	M	R	S	A
74-A	F	27	166	11.8	Sm	—	+	D	—	L	A
74-B	M	24	174	12.9	Sm	—	A	D	—	S	F
74-C	M	28	168	13.1	Sm	—	A	D	—	S	F
74-D	F	25	170	13.5	Sc	L	A	D	—	L	A
75-A	F	57	153	11.3	Sm	—	A	D	—	S	A
75-B	F	57	154	11.8	Sc	L	A	M	O	L	A
76-A	F	22	159	12.5	Sc	I	A	L	O	S	A
76-B	F	18	160	12.6	Sm	—	A	M	R	L	F
76-C	F	19	163	12.7	Cr	I	A	D	—	S	F
76-D	F	21	172	13.2	Sm	—	+	D	—	S	F
76-E	F	26	160	12.8	Sm	—	A	D	—	S	F
77-A	M	49	169	11.4	Sm	—	A	D	—	S	F
77-B	M	36	159	11.9	Sc	L	A	L	O	S	F
77-C	M	44	155	12.4	Cr	L	A	D	—	S	F
78-A	M	28	185	13.1	Sm	—	Sm	D	—	S	F
78-B	M	26	178	12.3	Sm	—	+	M	O	L	A
78-C	M	24	182	12.9	Sm	—	A	D	—	S	F
79-A	M	20	166	12.2	Sm	—	Sm	D	—	S	A
79-B	M	23	168	12.6	Sm	—	A	D	—	S	A
79-C	F	21	162	11.8	Sm	—	A	L	O	S	S
79-D	F	29	152	12.7	Sm	—	A	D	—	S	F

TABLE 6.—*Continued*

No.	Sex	Age	H	BBI	E-Str.	E-C	FR	HC-B	HC-R	HF	EL
80-A	M	27	181	13.2	Cr	I	Sm	D	—	L	F
80-B	M	23	177	12.6	Sm	—	A	D	—	S	F
80-C	M	22	166	12.7	Cr	I	A	M	O	S	F
80-D	M	21	181	12.8	Cr	I	A	D	—	L	F
81-A	M	25	178	12.7	Cr	L	Sm	L	O	S	A
81-B	M	27	167	13.7	Sc	L	+	L	R	L	F
81-C	M	21	175	12.7	Sc	L	Sm	L	R	S	F
82-A	M	33	162	12.1	Sc	L	+	L	O	S	F
82-B	M	27	173	13.0	Sc	L	+	L	R	S	A
82-C	F	28	158	13.1	Sc	I	A	L	O	L	A
82-D	F	31	160	12.7	Sc	L	+	L	O	L	S
82-E	M	25	174	12.7	Sc	L	A	L	R	L	F
83-A	F	27	165	12.7	Sm	—	Sm	L	O	S	A
83-B	F	24	161	12.5	Sc	I	+	M	O	S	F
83-C	F	32	170	12.8	Sc	I	Sm	D	—	S	F

APPENDIX I

Method of calculating standard deviation of sib-pair differences

A hypothetical series of two families of four members each has been used. The "data" have been constructed so as to depict a combination of linkage and a non-linkage correlation between the same traits. The linkage involves a two-unit difference in the dimension, greater size occurring with Y in the first family and with X in the second family. The non-linkage correlation produces a two-unit difference in the dimension, always in favor of greater size with Y.

ORIGINAL DATA			SIB-PAIRS ALIKE IN TRAIT			SIB-PAIRS DIFFERENT IN TRAIT				
						Corrected for group difference by short method			Corrected for group difference by long method	
No.	Trait	Dimension	No.	Difference in dimension	(Difference in dimension)^2	No.	Difference in dimension (Y-X)	(Difference in dimension)^2	Difference in dimension—group difference	(Difference in dimension—group difference^2
1-A	X	19	1-AB	± 1	1	1-AD	+ 5	25	+ 5 − 2 = 3	9
1-B	X	20	1-AC	± 2	4	1-BD	+ 4	16	+ 4 − 2 = 2	4
1-C	X	21	1-BC	± 1	1	1-CD	+ 3	9	+ 3 − 2 = 1	1
1-D	Y	24	2-BC	± 1	1	2-AB	− 1	1	− 1 − 2 = −3	9
2-A	X	22	2-BD	± 2	4	2-AC	0	0	0 − 2 = −2	4
2-B	Y	21	2-CD	± 1	1	2-AD	+ 1	1	+ 1 − 2 = −1	1
2-C	Y	22								
2-D	Y	23		0	12		+ 12	52	0	28
			$\frac{12}{6} = 2$ $\sqrt{2} = 1.4$ = standard deviation of sib differences			$\frac{+12}{6} = +2$ = mean difference, Y − X. $\frac{52}{6} = 8.7 - 2^2 = 4.7$ = variance of sib-pairs, corrected for mean Y − X difference. $\sqrt{4.7} = 2.2$ = standard deviation of sib differences.			$\frac{28}{6} = 4.7$ $\sqrt{4.7} = 2.2$ = standard deviation of sib differences	

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Clinical and Genetical Studies of Hypodontia

I. Premolar Aplasia, Hyperhidrosis, and Canities Prematura; A New Hereditary Syndrome in Man[1]

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INTRODUCTION

HYPODONTIA of the permanent dentition is a common condition in man. The communications on this subject, being in most instances reports of single clinical cases, are numerous. There will be no attempt to review this literature here. Most papers with a relevance to genetical questions have been reviewed by Cockayne (1933), Euler and Ritter (1940), and Gates (1946).

Frequency of Hypodontia in Man

In a population of 10,000 school children Dolder (1936) found congenitally missing teeth in 3.4 per cent. Werther and Rothenberg (1939) examined 1,000 children aged 3 to 15 years and found a frequency of 2.3 per cent. These figures do not include observations of third molars.

The most common type of hypodontia of the permanent dentition is aplasia of the third molar. Hellman (1936), who examined 433 students of the Dental School of Columbia University, found that 25.4 per cent missed 1–4 third molars. Moramarco (1930) and Thomas (1931) found the figures of 25 and 22 per cent, respectively.

The next common types are the absence of the upper lateral incisors and the second lower bicuspids. As for the upper lateral incisors an exceptional high frequency was found by Jöhr (1934) in an isolated Swiss population (33.3 per cent, see further discussion below). In a neighboring valley, Dietrich (1933) found the same anomaly in 2.4 per cent only. Röse (*op. cit.*, Gates), in surveys totalling 15,000 individuals, found degeneration or absence of the upper lateral incisors in 6 per cent for Scandinavia, in 2–4 per cent for central Europe, in 1.4 per cent in Greece and about 1 per cent for colored races. No figures seem to be available for the absence of bicuspids.

Etiology of Hypodontia

In a great number of investigations it has been shown beyond doubt that hypodontia in man is in most cases genetically controlled. This interpretation

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has been facilitated by the fact that in the majority of cases hypodontia is evidently due to autosomal dominant genes. Naturally in some cases exogeneous factors such as syphilis or dietary and endocrine disorders may be the cause of the destruction or impaired development of the tooth germ, but from a statistical point of view the importance of such factors has now been reduced to its true value.

As hypodontia has been observed most often in upper lateral incisors, third molars and second bicuspids, this has been spoken of as a phylogenetic reduction of the human dentition, presumably associated with a shortening of the jaws. This concept of an evolutionary tendency towards reduction seems obscure and was evidently not based on a full understanding of modern genetics.

It should be admitted that most communications on hereditary hypodontia are difficult to interpret as concerns the exact condition of the trait in different members of the same pedigree. In family research work we are often tempted to use anamnestic or catamnestic data as a basis for diagnosis, which in itself is a practice to be opposed by all means. Especially in relation to the condition of the teeth such data are practically useless. As the experience of this and other investigators in this special field indicates, ordinary people are uncertain as to how many teeth they should have. If they have a tooth extracted, after a couple of years they frequently forget that they ever possessed it. On the other hand, I have seen congenital absence of 6 or more teeth in patients who expressed great surprise when informed of their deficiency. This clearly emphasizes the need for careful examinations and study of dental impressions and radiograms. In this connection it is worth noting that among nearly 500 reports that I have consulted on the subject of human hypodontia only a very few include observations on more than one member of the same family or pedigree.

However, in all cases where an extensive examination of the family members was made, the hereditary nature of hypodontia has been apparent. As might be expected, the genotypical basis of hypodontia is apparently diverse. Not only is hypodontia caused by different genes with varying degrees of penetrance in different pedigrees, but aplasia of a special tooth group or even individual teeth may be transmitted in one family as an autosomal dominant and in another as a recessive or sex-linked trait.

The excellent work by Jöhr (1934) on a small Swiss isolate numbering 300 individuals should be emphasized here. As mentioned above, as many as 33.3 per cent of the individuals over nine years of age lacked lateral incisors or had such teeth of a defective type; about 18 per cent had both upper lateral incisors missing. It could be stated with considerable assurance that the defect was due to a simple dominant gene. Furthermore, all living individuals with the anomaly could be traced back to a common ancestor who lived in the middle of the eighteenth century. In a neighboring community almost com-

pletely isolated from the fore-mentioned one, the same anomaly appeared with a frequency of only 2.4 per cent (Dietrich, 1933).

Though apparently not fully realized by Jöhr, these observations constitute one of the best examples of human evolutionary differentiation under the combined action of mutation and geographical isolation. At first one might think that a dominant mutation which causes a defective development of a certain structure would not be in line with evolutionary divergence in man. Secondly, we are accustomed to think that dominant mutations having a slight effect in the heterozygous state will, when homozygous, usually cause gross abnormalities or non-viable zygotes. Undoubtedly such mutations occur in man as has been shown by Mohr and Wriedt (1919) and Böök (1950) for chondrodystrophic disturbances. However, as shown by Jöhr, this effect is not a general rule. In dominant aplasia of the upper lateral incisors, marriages between two affected parents might be expected to give rise to children with gross abnormalities of the dental structures. Such extreme defects were not observed. Thus, in terms of viability, this mutation does not seem to be selected against. This conception is quite in agreement with the high frequency observed in Jöhr's population.

A definition of defective or normal is often hardly possible. Usually we think of a defect as a deviation from normality measured in terms of frequency. Suppose that a population had changed so that 90 per cent lacked their upper lateral incisors. Certainly in this population the 10 per cent having these teeth would be considered as individuals with supernumerary teeth and, as such, abnormal.

It seems very reasonable to assume that most cases of hypodontia in man originally are due to mutations. As these have mostly a dominant character and as this trait, as far as we know, has no bearing whatsoever on viability or fertility, a relatively rapid spread in the population is easily understood. Consequently there is no need for more or less obscure speculation on "evolutionary trends."

Hypodontia in Ectodermal Syndromes

Several pedigrees have been described in which hypodontia is associated with other ectodermal defects, particularly of the skin and nails. These may be interpreted as manifold effects of a specific gene.

Congenital ectodermal dysplasia of the anhidrotic type was described in 1848 by Thurnam. The main features of this syndrome are a thin, dry and glossy skin, with aplasia of the sweat glands, thinning of the hair, and hypodontia of irregular type, or often total anodontia. It may be transmitted as a sex-linked recessive or an irregular dominant (for a discussion, see Helweg-Larsen & Ludvigsen, 1948).

A family in which four women showed anomalies in the development of hair,

eyes, teeth and nails was published by Sulzberger (1938). Aplasia moniliformis, keratosis pilaris and defective development of the teeth was described by Strandberg (1922), as a probably dominant trait. A most extreme type as concerns the dentition is the syndrome of Thadani (1934) in which the deciduous as well as the permanent teeth are missing in combination with thinned hair and aplasia of the sweat glands. This syndrome is inherited as a sex-linked simple recessive and was traced through six generations.

These examples will suffice to show that there is often a very close connection between hypodontia and defects of other ectodermal derivatives.

In a strict sense, a hereditary syndrome should be defined as a combination of signs and symptoms which are due to the effect of a specific gene. Naturally polymeric gene combinations may occur which give rise to symptom complexes, but here the analysis is hampered to such an extent that from a practical point of view such syndromes are less important.

THE PRESENT INVESTIGATION

In this communication a new ectodermal syndrome which is inherited as a simple autosomal dominant will be reported. The clinical signs consist of *aplasia in the bicuspid region, premature whitening of the hair*, and *hyperhidrosis*. This combination of symptoms is interesting not only because it clearly demonstrates the features of a hereditary syndrome *sensu strictu*, but also from the point of view of orthodontics.

With the exception of the second lower bicuspids, hypodontia of this region seems to be very rare. Only a few cases have been found in the literature. Claremont (1924) reports a male, 13 years old, who according to the radiograms had a total aplasia of all eight bicuspids; nothing is known about his family. In 1925 Clapham described a male, also 13 years old, with complete absence of all bicuspids, verified by X-ray. The family history showed that the father had two upper and four lower bicuspids missing. A paternal aunt was said to have upper laterals missing. Humble (1925) reports a 20 year old patient of unspecified sex, who according to radiograms lacked all bicuspids of the upper jaw. Persistant deciduous teeth were noted. A girl, 11 years old, who lacked all four second bicuspids was reported by Gathergood (1926). In this case the deciduous teeth persisted with the roots absorbed in the lower jaw. The diagnosis was verified by radiograms. Recently a pedigree of missing second bicuspids and third molars was reported by Erwin and Corkern (1949). Four individuals were examined clinically. The trait was interpreted as caused by a simple autosomal dominant gene. Otherwise our knowledge of genes operating on the bicuspid region does not seem to be very extensive.

Early graying may be considered as a form of partial albinism. Several pedigrees have been reported which clearly demonstrate autosomal dominant

inheritance (Hare, 1929; Serebrowskaya, 1929; Wölflin, 1938; Plummer, 1937). Premature whitening of the hair thus may be inherited as a separate entity.

Hyperhidrosis of the palmo-plantar type was reported by Siemens (*op. cit.*, Gates) in 3 monozygotic twin pairs, all concordant, and in 3 dizygotic pairs of which two were concordant and one discordant. This points to a possible genetic etiology.

Material

In 1947 Dr. A. Smilovits called to my attention one of his patients at a tuberculosis sanatorium near Lund. At the age of 22 years this man had completely white hair; furthermore, several members of his family had the same trait. On examination it was found that the patient also lacked all eight bicuspids, and he was considerably disabled by a severe hyperhidrosis. This patient served as the propositus for the genetic study, and he is designated ♂1 on the pedigree chart (fig. 1), which includes only the relatives of this man.

In the Church Registers his ancestors were traced back to the mother of his maternal grandfather (♀10), and later 125 descendants of this woman were traced (fig. 1). The study was also extended to all descendants of two brothers and one sister of ♀10, but since no signs of the present syndrome were found among living members of these lines, they have been omitted from fig. 1. In all, about 300 persons were registered in this investigation. Among the 172 members (including 47 spouses) shown in fig. 1, I was able to examine personally 63 individuals, as indicated on the pedigree chart. Since hypodontia in this family was constantly found in association with a conspicuous early graying of the head hair, and since the latter trait had been followed with great interest by members of this kindred, it seems very unlikely that further cases with hypodontia may have been missed.

Methods of Examination

Each of the 63 individuals mentioned above was given a combined clinical and odontological examination. The odontological examinations were in most cases performed by Hans Grahnén, D.D.S., Malmö, and I take this opportunity to thank him for his excellent cooperation and competent work. In a few cases, owing to geographical reasons, the examinations were kindly performed by local dentists whose assistance is acknowledged in the individual records, which follow. The examination consisted in inspection, complete radiograms and dental impressions. The extent of dental caries was noted, but it showed nothing of special interest.

In the clinical examination special attention was paid to ectodermal structures, such as the skin, hair and nails. Also, special search was made for symptoms and signs of endocrine disorders or vitamin deficiency, and a complete clinical history was taken.

CASES WITH PHC SYNDROME

For the sake of brevity, the clinical and genetical entity reported in this paper has been designated the *PHC syndrome*. In the individual records the following abbreviations have been used:

Pr+ aplasia of bicuspids conclusive
Pr? aplasia of bicuspids probable
H+ sweat hypersecretion conclusive
H− sweat hypersecretion absent
C+ premature whitening of the hair

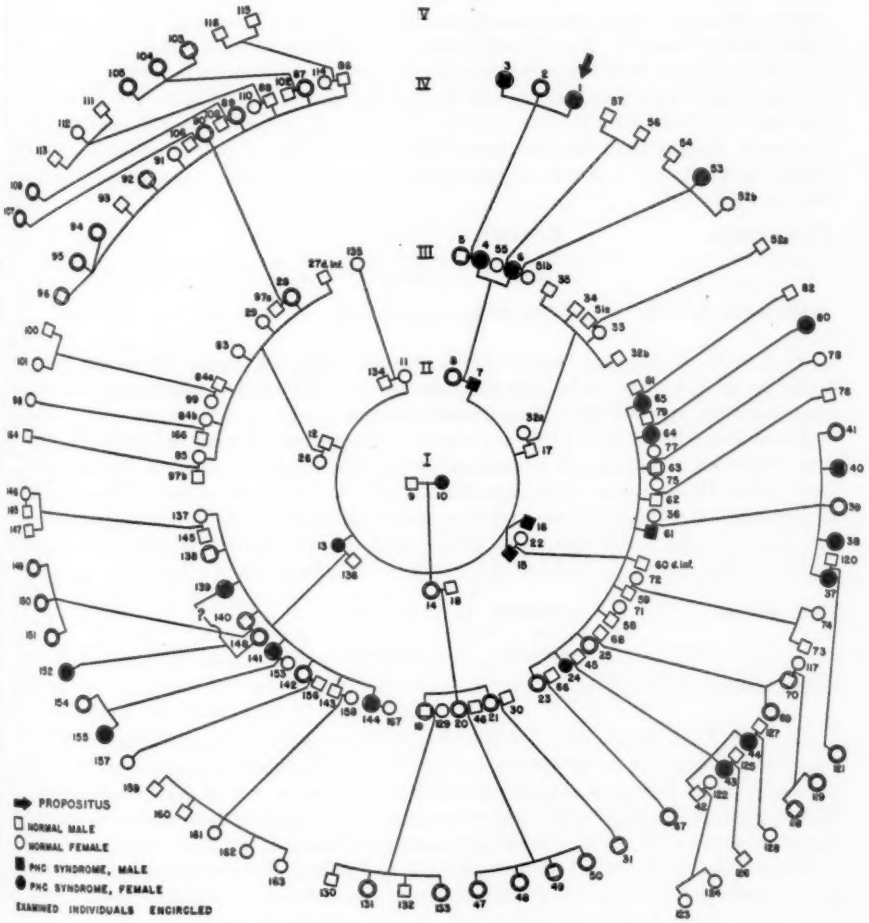

FIG. 1. Pedigree of family showing PHC syndrome.

In the dental formulae:

a aplasia r not erupted x extraction

No. 1. Propositus. (S. S.), male, born 15/8 1925. As a child morbilli, rubeola and epidemic parotitis without complications. Herpes zoster in 1939. Pulmonary tuberculosis found on routine X-ray examination in 1944. Since that time there has been no improvement in spite of hospital treatment. His tuberculosis is, however, of a benign type. Whitening of the hair started at the age of 7 years and was complete at age 20. His original hair color was blond. He has always been disabled by sweat hypersecretion, particularly of the palms and soles. His first dentition was quite normal.

Examination: 13/9 1947. Leptosome stature. Heart: normal findings. Blood pressure 120/70. Lungs: bilateral pulmonary tuberculosis (X-ray). No signs of endocrine disorders or vitamin deficiency. Neurological examination: normal findings. Eye fundi: normal. Wassermann reaction: negative. Mental examination: no psychopathological findings, intelligent. The patient did not show any subjective disorder with the exception of the excessive sweating. *Hair:* Head: total pigmentation loss. Axillary and genital hair: mixed white and blond. Eye brows and cilia normal. *Skin:* normal pigmentation, tanned. *Nails:* normal. *Irides:* blue-green. *Sweat glands:* Massive functional hypersecretion on palms and soles. *Blood groups:* O, N, Rh+, P+. *Teeth:* +3 was found in the place normally taken by +5 (fig. 2). Oral cavity normal.

Tooth formula:

876aa321	123aa67r
a76aa321	123aax7a

Diagnosis: Pr+ H+ C+ and pulmonary tuberculosis.

No. 3. (S. G. V. S.), male, born 10/7 1932. Always healthy. Whitening of the hair began at the age of 8, became successively more pronounced. Original hair color, black. Always annoying sweat hypersecretion. First dentition normal.

Examination: 10/10 1947. Ordinary physical and mental examination: negative. No signs of endocrine disorders or vitamin deficiency. Neurologically: negative. Normal eye fundi. *Hair:* Head: almost total pigmentation loss. Axillary hair: absent. Genital hair: mixed black and white. Eyebrows and cilia: normal pigmentation. *Skin:* normal pigmentation. *Nails:* normal. *Irides:* blue. *Sweat glands:* massive functional hypersecretion on palms and soles. *Blood groups:* A_1, N, Rh+, P+. *Teeth:* +03 persisted (fig. 3). Oral cavity normal.

Tooth formula:

r76aa321	12 03aa67r
a76aa321	12 3 aa6ra

Diagnosis: Pr+ H+ C+.

No. 4. (K. E. S.), female, born 6/7 1901. Except for the usual infectious diseases of childhood, always healthy. X-ray examination of the lungs in 1944 showed no sign of tuberculosis (the whole family was examined and positive findings occurred only in #1). Whitening of the hair began at the age of 8 or 9, complete at age 20. Always sweat hypersecretion disorders, more pronounced when she was younger. First dentition normal. Original hair color: blond.

Examination: 29/4 1948. Ordinary physical and mental examination: negative. No signs of endocrine disorders or vitamin deficiency. Neurologically: negative. Normal eye fundi. *Hair:* Head: total pigmentation loss. Axillary and genital hair: light brown. Eyebrows and cilia: normally pigmented. *Skin:* normal. *Nails:* normal. *Irides:* blue. *Sweat*

glands: functional hypersecretion on palms and soles. *Blood groups:* A_1, N, Rh−, P+. *Teeth:* 5−, 4−, −4, −5 always missing according to the patient. All teeth in the lower jaw had been extracted owing to paradentosis. +3 and 3+ were found in the places usually taken by +5 and 5+.

Tooth formula:

a7xaa321	123aa67a
xxxaaxxx	xxxaaxxx

Diagnosis: Pr+ H+ C+.

No. 6. (A. H. R.), male, born 21/9 1898. Always healthy. Original hair color dark brown. Whitening started at the age of 14–15 and was complete at age 21. The patient was not aware of any sweat disorders.

Examination: 21/4 1948. (E. M. Frick-Meijer, D.D.S.). Healthy. No abnormalities concerning physical or mental conditions. *Hair:* Head: complete pigmentation loss. Axillary and genital hair: normal. Eyebrows and cilia: normally pigmented. *Skin:* normal. *Nails:* normal. *Irides:* dark blue-grey. *Sweat glands:* No obvious hypersecretion. *Teeth:* First dentition unknown. Oral cavity normal.

Tooth formula:

876a4321	123 a5678
x7xaa321	123 aa67x

Owing to the extractions the number of bicuspids missing cannot be decided definitely, 6 being the most probable number.

Diagnosis: Pr+ H− C+.

No. 7. (G. H. P. R.), male, born 18/12 1875. Anamnestic data obtained from his daughter (#4): Whitening of his hair started at school age and was complete at age 20. It is very probable that he lacked several teeth but the informant cannot give accurate information. Nothing is known about his sweat glands.

Diagnosis: Pr? C+ H?.

No. 10. (L. C. D.), female, born 24/12 1831, died 1919. Anamnestic data obtained from one of her sons (#17): Nothing is known about her teeth. As a young girl she had black hair, which in a very short time turned white. At the age of 19 the hair was completely white.

Diagnosis: Pr? C+ H?

No. 13. (A. L. P.), female, born 20/7 1864, died 4/12 1943 of pneumonia. Anamnestic data obtained from her sons: Whitening of the hair began at about the age of 20, complete at age 30. Condition of her teeth is unknown.

Diagnosis: Pr? C+ H?

No. 15. (F. V. P. W.), male, born 21/10 1869. Emigrated to the U. S. A. in 1890. Anamnestic data obtained from his brother (#17): Whitening of the hair began at school age and was completed at 19 or 20. Condition of his teeth is unknown.

Diagnosis: Pr? C+ H?

No. 16. (C. O. B.), male, born 21/10 1869, the twin brother of #15. Emigrated to the U. S. A. in 1890. Anamnestic data obtained from his brother (#17). He was often mistaken

for his brother; most probably they were monozygotic twins. Presumably his hair turned white in the same way as in his brother. Conditions of his teeth unknown.

Diagnosis: Pr? C+ H?

No. 24. (N. E. S. A.), female, born 21/11 1892, died 13/10 1929 of an automobile accident. Anamnestic data obtained from her sister (#25): Whitening of the hair began very early. She was "silver white" when she died. She lacked several teeth, probably all the bicuspids.

Diagnosis: Pr? C+ H?

No. 37. (E. M. A.), female, born 15/10 1924. Scarlet fever at the age of two years, otherwise always healthy. Whitening of the hair started at the age of 6. No sweat disorders. Radiogram of the lungs in 1943 negative (pulmonary tuberculosis was discovered in her sister #38) at that time). First dentition normal. Original hair color: blond.

Examination: 21/1 1948. Ordinary physical and mental examination: negative. No signs of endocrine disorders or vitamin deficiency. Neurologically: negative. Normal eye fundi. *Hair:* Head: Grayish white. Almost total pigmentation loss. Axillary and genital hair: blond. No hypo- or hypertrichosis. Eyebrows and cilia: normal. *Skin:* Normal. *Nails:* Normal. *Irides:* blue. *Sweat glands:* No hypersecretion. *Blood:* Meinicke negative. *Teeth:* +03 persists. +3, 3+ and 3− displaced to the locus of 4. Slight deformities from rickets on 1+, +1 and 6+. Oral cavity normal.

Tooth formula:

r76aa3a1	12 03 3aa67a
r7xaa321	12 3aax7r

Diagnosis: Pr + H− C+.

No. 38. (K. E. W.), female, born 1/10 1925. As a child healthy. In routine X-ray examination, 1943, bilateral pulmonary tuberculosis was discovered. The patient had no subjective disorders. The radiogram showed patchiness on both apices of the lungs. The disease progressed slowly. In 1945, extrapleural pneumolysis and resection of costae IV dx was undertaken. The patient was sent home with oleothorax which she still had. She is now very improved, but still unable to work. There are at present no subjective disorders. There has been some nervousness in combination with this period of disease, but no real insufficiency. Whitening of the hair started at age 12–13. Original hair color: light brown. Always sweat hypersecretion disorders. First dentition normal.

Examination: 21/1 1948. General condition relatively good, a little pale. Heart and abdomen: negative. Lungs: pulmonary tuberculosis amb., with oleothorax. Neurologically: negative. Normal eye fundi. *Hair:* Head: light brown, about 50 per cent white, evenly mixed, no white spots. Axillary and genital hair: light brown, quantitatively normal. Eyebrows and cilia: normal. *Skin:* normal. *Nails:* normal. *Sweat glands:* moderate functional hyperhidrosis. *Irides:* blue. *Blood:* Meinicke negative. *Teeth:* 05+ persists. +3 displaced to the locus of +5. Bridge +3, +2. Oral cavity normal.

Tooth formula:

r76aa 05 321	123aa67r
r7xaa 321	123aax7r

Diagnosis: Pr+ H+ C+.

No. 40. (P. H. W.), male, born 29/5 1928. Always healthy. Examined for tuberculosis in 1943, no positive findings. Whitening of the hair started at age 12. Always sweat hypersecretion disorders. First dentition normal. Original hair color: light brown.

Examination: 22/1 1948: Ordinary physical and mental examination: negative. No signs of endocrine disorders or vitamin deficiency. Neurologically: negative. Normal eye fundi. *Hair:* Head: light brown, about 25 per cent white. Axillary and genital hair: normal. Eyebrows and cilia: normally pigmented, and quantity normal. *Skin:* normal. *Nails:* normal. *Irides:* blue. *Sweat glands:* Massive functional hyperhidrosis of palms and soles. *Blood:* Meinicke negative. *Teeth:* 03+ persists. +3 behind +03. No diastemata of the upper jaw. Oral cavity normal.

Tooth formula:

r76aa3 03 21	123aa67a
a76aa3 21	123aa67r

Diagnosis: Pr+ H+ C+.

No. 43. (G. S. H. L.), female, born 12/2 1917. Always healthy. Whitening of the hair started at age 10–11. All bicuspids were missing, according to a dentist. No hypersecretion disorders. First dentition normal. Original hair color: light brown.

Examination: 15/12, 1947. Healthy. Ordinary physical examination: negative. No signs of endocrine or vitamin disorders. *Hair:* Head: light brown, about 25 per cent white. Axillary and genital hair, eyebrows and cilia: normally pigmented, quantity normal. *Skin and nails:* normal. *Irides:* blue. *Sweat glands:* no hypersecretion. *Teeth:* Oral cavity normal. Partial prothesis of upper and lower jaw.

Tooth formula:

x6aaxxx	xxxaa6x
xxaa321	123aaxx

Diagnosis: Pr+ H− C+.

No. 44. (D. A. M. K.), female, born 12/10 1913. Always healthy. Whitening of the hair started at age 10–11. +3 was lost in Sept. 1947 and −5 erupted 1946. No sweat disorders.

Examination: 15/12 1947 (B. Holmboe-Sandberg, D.D.S.): Healthy. No physical or mental disorders. *Hair:* Head: red-blond, about 50 per cent white. Axillary and genital hair, eyebrows and cilia: normal. *Skin and nails:* normal. *Irides:* blue. *Sweat glands:* no hypersecretion. *Teeth:* Deep bite. Oral cavity normal.

Tooth formula:

a76aa321	1234567a
8x6aa321	123a5678

Diagnosis: Pr+ H− C+.

No. 53. (D. H. B.), female, born 11/6 1921. No diseases of childhood. At 17 a severe sciatic neuralgia. At present no subjective disorders. Had dark brown hair as a child: later it turned lighter and at age 14 the first white hairs were found. Thereafter depigmentation was progressive. Always sweat hypersecretion disorders.

Examination: 21/5 1948 (S. G. Blomqvist, D.D.S.): Healthy. No physical or mental disorders. *Hair:* Head: quite white. Eyebrows and cilia: normal. *Skin and nails:* normal. *Irides:* grey-light blue. *Sweat glands:* functional hyperhidrosis of axillary glands and soles,

less expressed on palms. *Teeth:* first dentition normal. 3+ and +3 have been extracted because of insufficient room.

Tooth formula:

87654x21 / 876a4321	12x45678 / 1234a678

Diagnosis: Pr+ H+ C+.

No. 61. (H. W. W.), male, born 7/1 1903, died of an automobile accident on 13/10 1929. Anamnestic data obtained from his wife and several sibs: At 17 or 18 his hair was quite white. There is agreement on the fact that he lacked all the bicuspids. Nothing is known with certainty about his sweat glands.

Diagnosis: Pr? H? C+.

No. 64. (G. W.), female, born 23/10 1909. Always healthy. She did not remember anything about diseases of childhood. Sweat hypersecretion disorders localized mostly on the forehead, less on palms and soles. The hair started to turn white at age 10–11. First dentition normal. Original hair color: light brown.

Examination: 26/1 1948. Physical examination of internal organs: negative. Neurologically: total anosmia. Mental examination: negative. Eye fundi: normal. *Hair:* Head: light brown, about 50 per cent white. Axillary and genital hair, eyebrows and cilia: normal. No hypo- or hypertrichosis. *Skin and nails:* normal. *Sweat glands:* functional hypersecretion, predominately of the forehead. *Irides:* blue. *Blood:* Wa.R. negative. *Blood groups:* A_1, MN, Rh+, P+. *Teeth:* Deep bite. Frontal diasthema of the upper jaw. Oral cavity normal.

Tooth formula:

8x654321 / 87xa4321	123a5678 / 123axx78

Possible aplasia of −5, though the patient thought that this tooth had been extracted.

Diagnosis: Pr+ H+ C+, and anosmia.

No. 65. (D. E. M. P.), female, born 3/3 1912. The patient did not remember any diseases of childhood. Previously always healthy. The last 4 or 5 years neuroasthenic disorders of psychosomatic type. Had a hysterical temper. She had been periodically insufficient. She complained of frigidity and the sexual aspects of her marriage were not satisfactory. Had a moderate eclampsia in 1943. Whitening of the hair started at age 12–13. No sweat hypersecretion disorders. First dentition normal. Original hair color: blond.

Examination: 22/1 1948. Healthy looking. Physical examination: negative. Mental examination: psychosomatic disorders, neurotic. Neurologically: negative. Eye fundi normal. No signs of endocrine or vitamin disorders. *Hair:* Head: blond, about 75 per cent white. Axillary and genital hair, eyebrows and cilia: normal. *Skin and nails:* normal. *Sweat glands:* nothing pathological. *Irides:* blue. *Blood groups:* B, MN, Rh+, P+. *Teeth:* Deep bite. Retrusion of the upper incisors. Infraocclusion on +4. Oral cavity normal. 03− and −03 persisted until age 20. Eruption of +5 at age 26.

Tooth formula:

r76543xl / a7xar321	123r567a / 123aa67r

Diagnosis: Pr+ H− C+.

No. 80. (M. N. L. W.), female, born 1/8 1931. Diptheria and scarlet fever without complications at school age. Otherwise always healthy. Observed the first white hair at age 15. Original hair color: blond. Always sweat hypersecretion disorders. Complaints of insufficient ability to taste and smell. First dentition normal.

Examination: 26/1 1948. Healthy looking. Ordinary physical and mental examination: negative. Neurologically: complete anosmia, but normal taste. Eye fundi: normal. *Hair:* blond, about 25 per cent white. Axillary and genital hair, eyebrows and cilia: normal. No hypo- or hypertrichosis. *Skin and nails:* normal. *Irides:* blue. *Sweat glands:* massive functional hyperhidrosis, predominately of soles and exillae. *Blood groups:* O, MN, Rh+, P−. *Teeth:* 03+, +03, and −03 persist; +3, 3+ and −3 are distal to the corresponding deciduous teeth (figs. 4, 5). Oral cavity normal.

Tooth formula:	a76aa3 03 21	12 03 3aa67r
	r76aa3 21	12 03 3aa67r

Diagnosis: Pr+ H+ C+, and anosmia.

No. 139. (N. S. N.), male, born 23/4 1893. Previously healthy. Last 10 years nephrolithiasis disorders. Admitted to a surgical clinic in 1938, only internal treatment. Complains of rheumatic disorders for the last two years; nothing serious. Whitening of the hair started at age 23 and was complete at age 30. Always sweat hypersecretion disorders. It is not possible to get exact information about his teeth, but he "remembers" that +03 was extracted at age 20 and 4− erupted at age 30.

Examination: 16/6 1948. Healthy looking. Ordinary physical and mental examination: negative. No joint engagements. Neurologically: negative. *Hair:* Head: quite white, a little thin. Axillary and genital hair: white. Eyebrows: blond, none white. Cilia: normal. *Skin and nails:* normal. *Sweat glands:* massive functional hyperhidrosis of palms and soles. *Irides:* blue-grey. *Blood group*: A_1. *Teeth:* Marked abrasion 3− ··· −3. Diastema between 3+ and 2+ about 1 mm. when 3+ was extracted one year ago. −3 and 3− at their normal loci. According to the radiograms only 4− is left. The aplasia is of course not absolutely certain, owing to the extractions.

Tooth formula:	?7xaax21	1x3aa67?
	x7xa4321	123aax7x

Diagnosis: Pr+ H+ C+.

No. 141. (A. E. N.), male, born 11/2 1898. Always healthy. Whitening of the hair started at 18. Original hair color: blond. No sweat hypersecretion disorders. At age 24 a deciduous tooth was extracted, probably +03; later +3 erupted. No definite information available concerning bicuspids.

Examination: 2/3 1948. Ordinary physical and mental examination: negative. Neurologically; negative. *Hair:* Head: quite white. Axillary and genital hair: brown with about 50 per cent white. Eyebrows and cilia: white. *Skin and nails:* normal. *Sweat glands:* No pathological findings. *Irides:* blue. *Blood groups:* A_1, MN, Rh−, P+. *Wassermann reaction:* negative. *Teeth:* all extracted except 7+, 1+, +1, +2, +3, +4; 3− ··· −4, −7.

Diagnosis: Pr? H− C+.

No. 144. (H. F. N.), male, born 29/6 1907. Had hepatitis some years ago, otherwise always healthy. Whitening started at age 20 and was complete at age 30. No sweat disorders. First dentition normal.

Examination: 22/2 1948. Healthy. Ordinary physical and mental examination: negative. Neurologically: negative. *Hair:* Head: quite white. Axillary and genital hair: 50 per cent white. Eyebrows and cilia: white. *Skin and nails:* normal. *Sweat glands:* No pathological findings. *Irides:* blue. *Teeth:* 05– and –05 persisted until age 24. A little later 5– erupted. Oral cavity normal.

Tooth formula: $\frac{87x54321}{87654321} \mid \frac{12345678}{1234a678}$

Diagnosis: Pr+ H– C+.

No. 152. (R. H.), female, born 3/7 1925. As a child, morbilli, rubeola and epidemic parotitis; nothing serious. Otherwise always healthy. As a girl dark, almost black, hair. Whitening started at age 21, progressing rapidly. Annoying sweating of palms.

Examinations: 21/5 1948. A little pale, otherwise healthy looking. Ordinary physical examination: negative. Neurologically: negative. Eye fundi: normal. Mentally: vagotone type, asthenic, with tendency to hypochondric reactions. Some vasolability. *Hair:* Head: 75 per cent white. Original hair color could not be determined owing to earlier bleaching; was said to have been dark. Axillary and genital hair: about 50 per cent white. Eyebrows and cilia: normal. No hypo- or hypertrichosis. *Skin and nails:* normal. *Sweat glands:* functional hyperhidrosis especially of palms. *Irides:* blue. *Blood groups:* A_1, N, Rh+, P+. *Teeth:* First dentition normal. 3+ and +3 displaced about 1 mm. distally.

Tooth formula: $\frac{a7xaa321}{r76aa321} \mid \frac{123aax7a}{123aa678}$

Diagnosis: Pr+ H+ C+.

No. 155. (G. D. N.), female, born 17/4 1934. Scarlet fever at age 4; no complications. Later healthy. She had not observed any whitening of the hair until it was pointed out to her. Always sweat hypersecretion disorders. First dentition normal.

Examination: 2/3 1948. Healthy looking. Ordinary physical and mental examination: negative. Neurologically: negative. No sign of endocrine or vitamin disorders. *Hair:* Head: slight but definite early whitening. Hair color: blond. Axillary and genital hair: normal, blond. Eyebrows and cilia: normal in quantity and pigmentation. *Skin and nails:* normal. *Sweet glands:* massive functional hyperhidrosis of palms and soles. *Irides:* blue. *Blood groups:* AB, N, Rh–, P+. *Wassermann reaction:* negative. *Teeth:* some deciduous teeth persisted "relatively long". Oral cavity normal.

Tooth formula: $\frac{r76r4321}{r76a4321} \mid \frac{1234r67r}{1234a67r}$

Diagnosis: Pr+ H+ C+.

Family members showing no symptoms of the PHC syndrome

The following members of the family have been examined and found healthy and in every respect normal. As there is no intention of analyzing the complete dental status of

the family, but only the hypodontia, the individual records have been omitted. The examined members are: Nos. 2, 5, 8, 20, 21, 28, 31, 39, 41, 47, 48, 49, 50, 69, 70, 87, 89, 90, 92, 94, 95, 96, 103, 104, 105, 107, 109, 119, 121, 131, 133, 138, 140, 148, 150, 151, and 154.

Some family members who were examined showed diseases or abnormalities which may be mentioned briefly:

No. 14. (T. R.), female, born 30/4 1867, had a severe paradentosis and lost all her teeth at 60. She also had rheumatoid arthritis.

No. 19. (P. H. R.), male, born 22/4 1901, had emphysema and bronchial asthma. Severe paradentosis.

No. 23. (T. H.), female, born 13/5 1891. Paradentosis.

No. 25. (G. S. G. A.), female, born 2/10 1894. Paradentosis. Neurasthenia.

No. 63. (E. V. V. W.), male, born 24/5 1907. Severe paradentosis.

No. 67. (M. H.), female, born 1912. Had a severe head contusion at the age of 10 and was unconscious for some minutes; developed a clear postraumatic neurosis. Headaches, unbalanced, and several organ symptoms. Periodically at work. At the examination 26/3 1948 she showed moderate symptoms. Ordinary physical examination: negative. Neurologically: negative. She always had an hysterical personality.

No. 118. (P. R. B.), male, born 2/5 1945, had a slight strabismus convergens.

No. 142. (O. P.), female, born 21/5 1900. Had a neurasthenic and hysterical personality with periods of insufficiency.

For all the other persons shown in the pedigree who had not been accessible to personal examination, anamnestic data were obtained from near relatives (parents, sibs or children). In no case has there been a report of any symptoms of the PHC syndrome.

A Question of Paternity

Early in this investigation it was obvious that the PHC syndrome was dependent upon a simple dominant autosomal gene. Also, the penetrance of this gene seemed to be relatively strong; no skipping of generations was observed. The intention of examining those persons and families who were said to be normal, however, lead to the discovery of a case (#152, described above) whose parents were both unaffected. The records of this family are as follows.

No. 140. (A. F. N.), the father of #152, born 22/9 1895. Always healthy. His first gray hair appeared at 40. The first and permanent dentitions were normal. He denies that any teeth had been missing. He never had any sweat hypersecretion disorders. All teeth of the upper jaw had been extracted 6 weeks before the examination.

Examined 20/5 1948. Healthy. Ordinary physical and mental examination: negative. Neurologically: negative. *Hair:* Head: blond, a little grey corresponding to his age. Axillary and genital hair, eyebrows and cilia: normal. *Skin and nails:* normal. *Irides:* blue-grey. *Sweat glands:* no hyperhidrosis. *Blood groups:* O, MN, Rh−, P+. *Teeth:* a radiogram of the upper jaw showed clearly the presence of alveoli of all bicuspids.

Tooth formula:

xxxxxxxx	xxxxxxxx
x7654x21	1234567x

There are evidently no symptoms of the PHC syndrome in this case.

No. 148. (E. N.), the mother of #152, born 16/8 1895. Since 18 years she had a moderate bronchial asthma. Amputation of the left breast for cancer in 1940. Complained of dyspnoea and heart disorder. Slight graying of the hair at 50. No hypersecretion disorders.

Examination: 20/5 1948. Lungs: emphysema with typical asthmatic breathing. Heart: enlarged to the left. Blood pressure 230/120. *Hair and sweat glands:* normal. No hypodontia. *Blood groups:* B, MN, Rh+, P+. No symptoms of the PHC syndrome.

Diagnosis: Bronchial asthma and arterial hypertension.

No. 149. Female, born 12/1 1916. Healthy as a child. As pulmonary tuberculosis was discovered in her sister (№ 150) the whole family was examined in 1941, with positive findings in her case: no cavities; ambulant symptomatic treatment; improved, but still under control. Subjectively healthy.

Examination: 16/6 1948. Hair, sweat glands, and teeth: normal.

Diagnosis: pulmonary tuberculosis.

No. 150. Female, born 27/1 1919. Admitted to Community Hospital, Malmö, in 1941, 1943, and 1944. Diagnosis: Pulmonary tuberculosis. In 1943 she developed a cavity and was treated with pneumothorax. She was considerably improved, but is still under ambulant treatment. *Examination:* 16/6 1948. Hair, sweat glands, and teeth: normal. *Diagnosis:* pulmonary tuberculosis.

No. 151. (K. L.), female, born 7/9 1920. Always healthy. Radiograms of the lungs in 1941 negative.

Examination: 16/6 1948. Hair, sweat glands, and teeth: normal. Healthy.

The appearance of the daughter, № 152, having the complete PHC syndrome seemed at first confusing because both parents were normal. The evidence for simple dominant inheritance was strong enough to question the legitimacy of the child. Also it seemed almost certain that the actual father should be found in the present pedigree of PHC syndrome, since the latter is a very rare abnormality. Fortunately the examination of the blood groups settled the question. As the presumptive father was O, the mother B, and the child A_1, it was obvious that № 140 was not № 152's father. There is reason to believe that № 152 was the child of her legal father's brother, № 139, who, as shown in fig. 1, had the PHC trait.

Clinical Analysis

The eighteen cases shown in table 1 are available for a closer clinical analysis and discussion.

The general health of the patients was good with the exception of the propositus, № 1, and a second cousin, № 38, both having pulmonary tuberculosis of a relatively benign type. The occurrence of two additional cases of tuberculosis in the pedigree (№ 149 and № 150) may be interpreted as possible evidence for the presence of a tuberculous predisposition of the family, or, it may be a mere coincidence. The data give no clear evidence favoring the assumption of a connection between the PHC syndrome and susceptibility to tuberculosis.

The neurological examinations revealed no pathological findings, except in № 64 and № 80 (mother and daughter) both of whom completely lack the ability to smell. The cause of this deficiency is unknown.

The eye fundi were examined with a common ophthalmoscope in ten cases. The findings were in all cases completely normal.

There was no evidence of a connection between the PHC syndrome and any mental aberration. Some asthenic traits were found in #38, and hysteria in #65. In the former case the nervousness evidently was due in large part to the presence of tuberculosis. Otherwise all the relatives were intelligent and quite normal people.

Since anodontia in earlier accounts had frequently been attributed to syphilis, vitamin deficiency, and endocrine disorders, special interest was devoted to these points. In seven cases it was possible to get a blood specimen for a Wassermann or Meinicke reaction. The specimens were examined at the

TABLE 1. SUMMARY OF 18 EXAMINED PATIENTS WITH THE PHC SYNDROME
P = premolar aplasia, C = canities prematura, H = hyperhidrosis.

CASE NO.	SEX	AGE	SYMPTOMS PRESENT	NUMBER OF MISSING PREMOLARS	NUMBER OF UNERUPTED PREMOLARS	NUMBER OF MISSING 3RD MOLARS	AGE OF ONSET OF WHITENING OF THE HAIR
1	♂	23	P, H, C	8	0	2	7
3	♂	16	P, H, C	8	0	2	8
4	♀	47	P, H, C	8	0	2	8
6	♂	50	P, C	6?	0	0	14
37	♀	24	P, C	8	0	1	6
38	♀	23	P, H, C	8	0	0	12
40	♂	20	P, H, C	8	0	0	12
43	♀	31	P, C	8	0	?	10
44	♀	35	P, C	5	0	2	10
53	♀	27	P, H, C	2	0	0	14
64	♀	39	P, H, C	3	0	0	10
65	♀	36	P, C	3	2	2	12
80	♀	17	P, H, C	8	0	1	15
139	♂	55	P, H, C	7?	0	?	23
141	♂	50	P, C	?	0	?	18
144	♂	41	P, C	1	0	0	20
152	♀	23	P, H, C	8	0	2	21
155	♀	14	P, H, C	2	2	0	14

Bacteriological Institute, University of Lund, through the courtesy of Prof. A. Lindau. The tests were all negative.

Signs of vitamin deficiency were found in only one case, #37. This patient had rickets as a child, and changes typical of rickets were found in some of her teeth. No positive findings were noted in the other patients, nor was there any history of rickets in other affected members of the kindred. Also, clinical signs of endocrine disorders were invariably absent. In fact, analysis of the anamnestic data gave no evidence that diseases of infancy or childhood or any other disease could be considered as the cause of the PHC syndrome.

In conclusion, no evidence was found for the presence of any exogenous factor having a connection with the PHC syndrome.

Symptomatology of the PHC Syndrome

Canities prematura. Early whitening of the hair is the most constant symptom, being found in every case. The onset and expression of this feature was somewhat variable, however. The age of onset varied from 6 to 23 years. The whitening was uniform and was never seen to occur in spots. Most constantly the hair of the head was affected. The progress of whitening was usually slow, but in the older individuals it had always led to complete pigmentation loss. In some cases (6 out of 18) there was conspicuous whitening of other parts of the body such as the axillary and genital hair, and the eyebrows and cilia. With the exception of this depigmentation, the hair was completely normal. No tendency to hair diseases or baldness was observed. The distribution of the hair over the body was quite normal. Neither hypo- nor hypertrichosis was observed, which is a point of particular interest since such disturbances are often met with in patients with hypodontia.

Accurate information about the original hair color was obtained in 16 cases, as follows:

Blond	Light brown	Dark brown	Red blond	Black	Total
7	4	3	1	1	16

So far it has not been possible to analyze the nature of the depigmentation. However, from a biochemical point of view there must be some deficiency of melanin formation. Apparently this deficiency is not of a primary type as found in certain cases of albinism, where it may be assumed that some co-enzyme is completely lacking. In PHC syndrome the pigment formation is originally within the normal range of variation. Later it ceases, very much in the same way as during normal ageing. Furthermore, the pigmentation of the skin is never affected.

Eye color. All 18 affected individuals had blue irides. As this is a very common trait in Sweden it may be a mere coincidence. However, considering that these patients have a deficient production of hair pigments, a connection with iris pigmentation might be possible. This deficiency may be of the same nature as in phenylpyruvic amentia, although taking place at another level. As is well known, patients affected with the latter disease are often characterized by light hair and blue irides.

Hyperhidrosis. Two-thirds of the patients showed a definite functional abnormality of the sweat glands. Functional hyperhidrosis is a comparatively common symptom especially in psychosomatic cases, although here the disorders are usually mild. In the present kindred showing PHC syndrome, the abnormality constituted a definite pathological trait; the hyperhidrosis was of a massive type constituting a real disadvantage to the patient in many situations. It was not particularly related to nervousness or mental upset. In most

cases the hyperhidrosis was of the common palmoplantar type. In a few patients there were other affected skin areas, such as the axillae and forehead, but here the disorder was less pronounced. In 45 normal members of the family

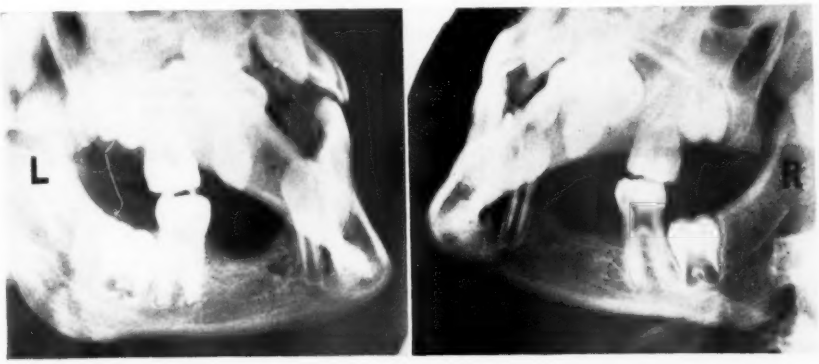

FIG. 2. Case no. 1, the propositus. Radiograms of upper and lower jaw, showing aplasia of all bicuspids. Taken 1936 at the age of 11 years.

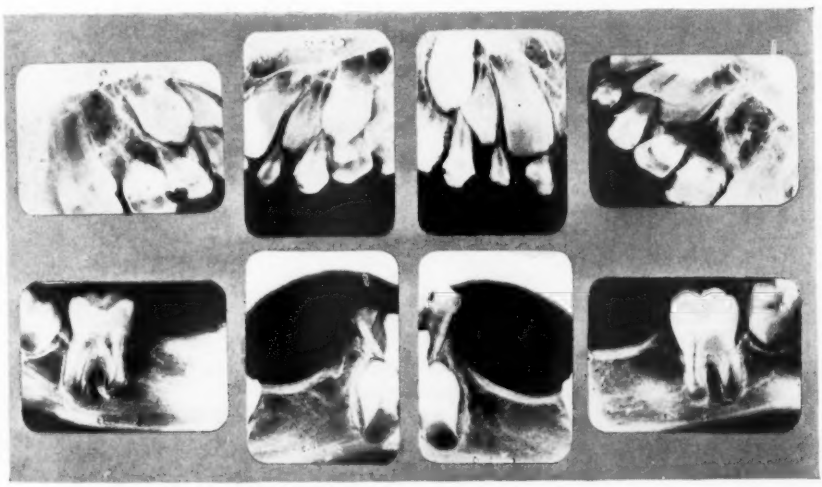

FIG. 3. Case no. 3, the brother of the propositus. Radiograms taken at the age of 8 years, showing aplasia of all bicuspids.

no symptoms of hyperhidrosis were found. Consequently this trait may be considered an integral part of the PHC syndrome.

Hypodontia. Radiograms were taken in 16 cases and dental impressions in 14. These examinations were omitted in some cases because of too many extractions. The most striking feature was the affection of the bicuspid region. In

nine patients all 8 bicuspids were missing and no anlagen could be detected in the radiograms (cf. figs. 2–5). One patient lacked 5 bicuspids, two lacked 3, another lacked 2, and one lacked only 1 bicuspid. These cases were all demonstrated conclusively by X-rays. In three other cases the exact number of missing bicuspids could not be determined. These patients were between 50 and 55 years old and had had several teeth extracted; they could not supply exact information about their extractions, nor could their dentists, inasmuch as the latter generally do not put such simple operations on record. In two cases, ♯65 and ♯155, two bicuspids had not erupted.

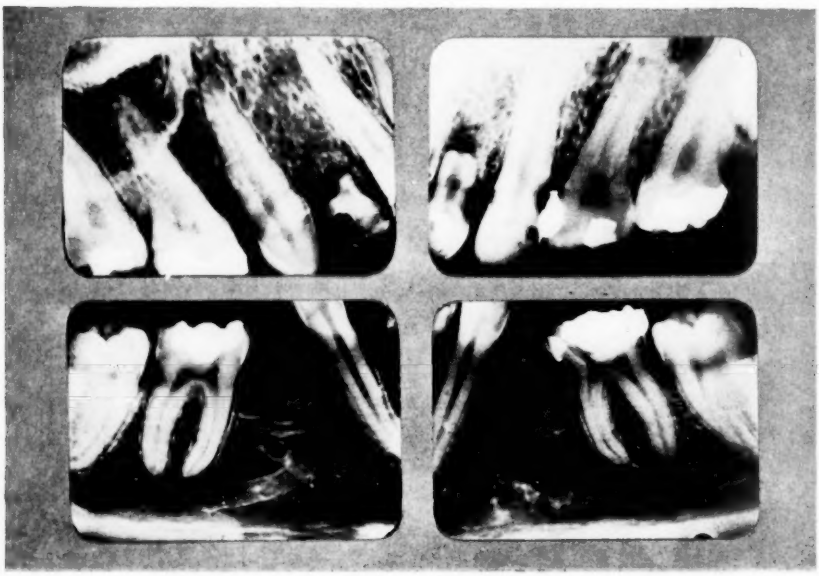

FIG. 4. Case no. 80. Radiograms taken at the age of 17 years. Aplasia of all bicuspids, persistence of 03+, +03, and −03. Note the distal displacement of the canines.

In at least 50 per cent of the individuals showing PHC syndrome 1 or 2 third molars were lacking. As will be discussed below, there is no reason to believe that this type of aplasia, which is a very common trait in the general population, has any connection with the aplasia of the bicuspid region. We are evidently concerned here with a dominant gene selectively affecting the bicuspid region. This is of particular interest as it points to the fact that different groups of teeth normally may be controlled by different genes.

Secondary effects of hypodontia. In most of the youngest patients persistent deciduous teeth were found. In five cases aged 15–23 years (♯3, 37, 38, 40, and 80), the following teeth were found: +03, 03+, −03 and 05+. In three

other patients (※ ※44, 65 and 144), a history of persistent teeth was obtained. Individual ※44 still had +03 at 34 years, ※65 had 03− and −03 at 20 years of age, and ※144 had 05− and −05 at 24. As the resorption of the roots of the deciduous teeth is mainly an effect of pressure from the growing permanent teeth, the persistence of these deciduous teeth until adult age would be anticipated in such cases of premolar aplasia.

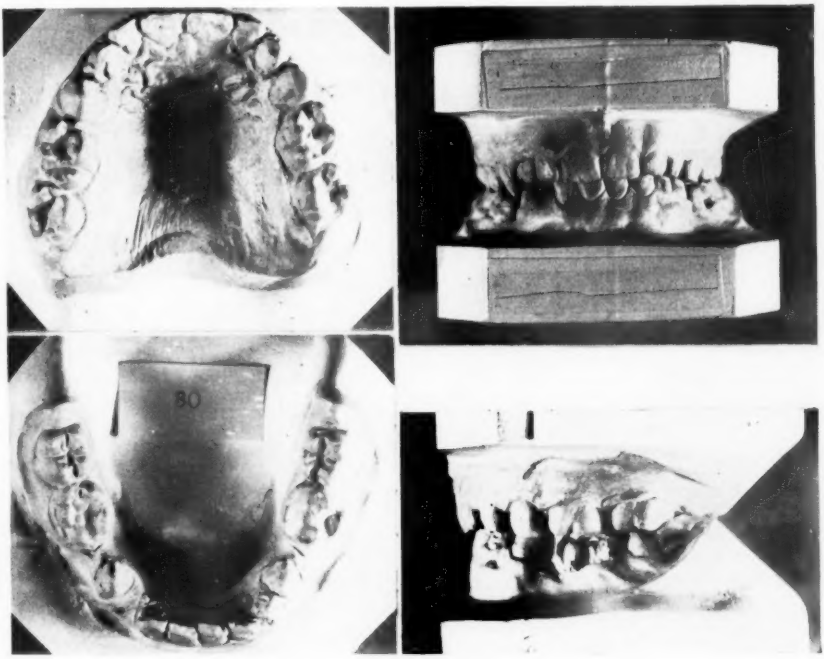

FIG. 5. Dental impressions of No. 80. Compare with fig. 4.

Another secondary effect, perhaps more interesting, is the displacement of the canines. In ten cases, one or more of the canines were found at varying distances distal to their usual locations. Four patients thus had +3 or 3+ in the place usually taken by +5 and 5+, respectively. Persistent deciduous teeth and a backward dislocation of some of the canines are thus characteristic features which can be interpreted as purely secondary effects of bicuspid aplasia.

The clinical analysis has shown that the symptoms of bicuspid hypodontia and premature whitening of the hair were constantly found in these patients. The third symptom, hyperhidrosis, was characteristic, but was present in only two-thirds of the cases.

Genetic Analysis

For an analysis of the transmission of the PHC syndrome 10 families are available in which the condition is transmitted without skipping a generation. Thus dominance is evident. The hypothesis of a simple dominant autosomal gene is tested by comparing the observed ratios of affected and normal children in the sibships arising from matings, involving an affected parent (table 2). After making allowance for the selective nature of the data by excluding the propositus, his mother, and his maternal grandfather from their respective sibships, the resulting ratio, 24 affected:19 normal, is found to be in satisfactory agreement with the expected 1:1 ratio. Also, the sex distribution

TABLE 2. SIBSHIPS HAVING ONE PARENT WITH PHC SYNDROME

Sibships are listed by number of the affected parent, as indicated in figure 1.

CHILDREN OF CASE NO.	NORMAL SIBS	SIBS WITH PHC SYNDROME	TOTAL
4	1	1*	2
6	2	1	3
7	0	1**	1
10	4	3***	7
13	5	3	8
15	7	4	11
24	1	2	3
61	2	3	5
64	1	0	1
141	1	1	2
Total	24	19	43

* Omitting the propositus, #1.
** Omitting the propositus' mother, #4.
*** Omitting the propositus' grandfather, #7.
χ^2 (1:1 ratio) = $(24 - 19)^2/43 = 0.581$, D.F. = 1, $0.3 < P < 0.5$.

among all affected persons in the pedigree is normal, viz. 11 ♂:14 ♀, so that there is evidently no preference for either sex.

Further analysis of the pedigree gives no evidence of independent segregation of the three traits comprising the syndrome; polymeric factors or genetic linkage thus seems to be out of the question. Transmission from father to son in 3 instances also excludes the possibility of ordinary sex-linked inheritance.

There remains to be tested only the possibility of partial sex-linkage, that is, transmission of the gene in the homologous segments of the X and Y chromosomes. For this purpose the progeny of affected males having parents of known genotypes must be examined. Under partial sex-linkage, a man who inherits the trait from his mother has the genotype X^AY^a and if he inherits from his father he is X^aY^A. Assuming less than 50 per cent crossing-over, we would then expect X^AY^a males to transmit the syndrome preferentially to daughters, while X^aY^A would transmit it preferentially to sons.

The pedigree (fig. 1) is seen to contain 6 sibships having an affected father and in each case the affected paternal grandparent is known. In 4 cases the affected father is X^AY^a and in 2 cases X^aY^A. The children resulting from these unions are as follows:

CHILDREN OF:	AFFECTED DAUGHTERS	NORMAL SONS	AFFECTED SONS	NORMAL DAUGHTERS
X^AY^a males (#7, 15, 139, 141)	$b = 6$	$b = 4$	$a = 2$	$a = 3$
X^aY^A males (#6, 61)	$a = 3$	$a = 1$	$b = 1$	$b = 3$

In this table, one son (#60) of case #15 has been excluded, since this child died in infancy.

In the event of partial sex-linked inheritance, the members in the 4 cross-over classes (designated by a in the above table) are expected to total less than the non-cross-overs (b). The proportion of cross-overs is in fact 9/23, so that the deviation is in the direction favoring the hypothesis. However, the deviation from the 1:1 ratio expected in the absence of linkage is not significant:

$$\chi^2 \text{ (1:1 ratio)} = (14 - 9)^2/23 = 1.09, \quad \text{D. F.} = 1, \quad P = 0.30.$$

It therefore seems more probable, on *a priori* grounds, that the gene is located in one of the autosomes.

As far as could be discovered the main effects of this gene are upon the premolar teeth, the hair color, and the sweat glands. The penetrance of the gene is evidently strong. For hypodontia of the premolar region and premature whitening of the hair the penetrance is doubtless 100 per cent. The third symptom, sweat hypersecretion, is less stable, being present in about two-thirds of the cases only.

The expression of the gene shows a certain intrafamilial variability. The effect on the premolar region is always hypodontia, but the number of missing teeth varies somewhat, as is shown in table 1. It should be stressed, however, that the effect seems to be limited specifically to this one region. In two cases retained premolars were noted; the material is too small to decide whether these cases illustrate a slight effect of the gene for PHC syndrome or whether their occurrence is coincidental. As concerns the third molars, I think it unjustified to base any conclusion on the fact that 50 per cent of the examined persons lacked one or two of these teeth as revealed by X-ray studies. Considering that a frequency of about 25 per cent has been found in extensive surveys of unselected persons, it is probable that the higher percentage observed in this small series is merely coincidental.

The expression of the premature whitening of the hair is variable too. The whitening showed considerable variation in its time of onset (table 1). However, in all cases the process was definitely premature.

The fact that a gene may selectively affect a special group of teeth is of considerable interest from a genetical as well as from an embryological point

of view. From other studies it is known that genes may more or less selectively affect the lateral or the central incisors, as well as those causing complete anodontia or more general disturbances. This may be interpreted to mean that different groups of teeth constitute different embryological units. On the other hand, it seems justifiable to assume that certain genes are necessary for tooth formation and development in general. But, in addition, special genes seemed to be involved in the development of certain groups of teeth, and this specialization may even extend to certain individual teeth.

SUMMARY

1. A new hereditary syndrome has been described under the designation of *PHC syndrome*; it includes: (P) hypodontia of the premolar region, (H) hyperhidrosis of the palms and soles, and (C) premature whitening of the hair (canities prematura).

2. The PHC syndrome was studied in a kindred with 172 members of which 25 were affected. Sixty-three persons were submitted to thorough clinical and odontological examinations. The collected evidence indicates that this syndrome is caused by a simple autosomal dominant gene.

3. The clinical analysis was based on 18 completely examined individuals. Nine patients lacked all 8 bicuspids; the others were missing 1 to 7 of these teeth. In most cases there was a displacement backwards of the canines, and an additional secondary effect was noted in the form of persistent deciduous teeth in all cases. Hyperhidrosis was severe in 12 cases.

4. The penetrance of this gene as concerns hypodontia and early graying is complete, with no difference observed between the sexes. The expressivity is somewhat variable as to the number of missing bicuspids and the age at which the whitening of the hair begins.

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Familial Hypoglycemosis of Probable Genetic Origin

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HEREDITY has been demonstrated to play an important role in a vast number of medical disorders. In fact it is unusual to encounter a disease, particularly one of non-microbic origin, in which heredity has not been mentioned as a possible contributing cause. Thus, the appearance of familial cases of spontaneous hypoglycemosis (hypoglycemic state) seems worthy of report, since it is possible that genetic factors are being overlooked in the study of this metabolic disorder.

A review of the literature on hypoglycemia reveals few references to any familial or hereditary tendencies. Hartmann and Jaudon (1937) mention the occurrence of the disease in father and son, citing the similarity in insulin sensitivity tests, but do not comment further upon this association. Bertoye, Bertoye, and Malot (1948) suggest that hypoglycemia, as well as other disorders such as migraine and vagotonia, all depend upon the same familial diathesis. In mice, hypoglycemia, as well as hyperglycemia, has been described as a hereditary recessive trait by Cammidge and Howard (1930). Hyperglycemia, a central feature of diabetes mellitus, is a well-known hereditary defect of metabolism in man.

During the past two years, two families with multiple cases of non-Addisonian spontaneous hypoglycemia have been studied in the Pediatric Department of the University of Minnesota Hospital. The studies have dealt primarily with the dynamics of this metabolic disorder, and especially with the use of adrenocorticotropic hormone (ACTH) in its treatment (McQuarrie *et al.*, 1949). In view of the familial character of the disorder, it was felt that a study of other members of the family might reveal subclinical disturbances which would help in elucidating a possible genetic factor underlying the familial occurrence of the disease. Therefore, various chemical tests such as fasting blood sugar, glucose tolerance curves, and insulin sensitivity tests, have been carried out on other members of the family. This approach is similar to that which has been used in the study of relatives of diabetics. A brief report of the results of this study follows.

As shown in the accompanying pedigree (figure 1), the affected members in Family *A* are three brothers, whose ages range from two to five years. They

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are similar in appearance, and all show convergent strabismus, mild ataxia, and a moderate degree of mental retardation. The parents know of no similar disease among their relatives. The only other circumstance of possible genetic significance is the fact that both the maternal and paternal grandparents lived in the same Swedish province.

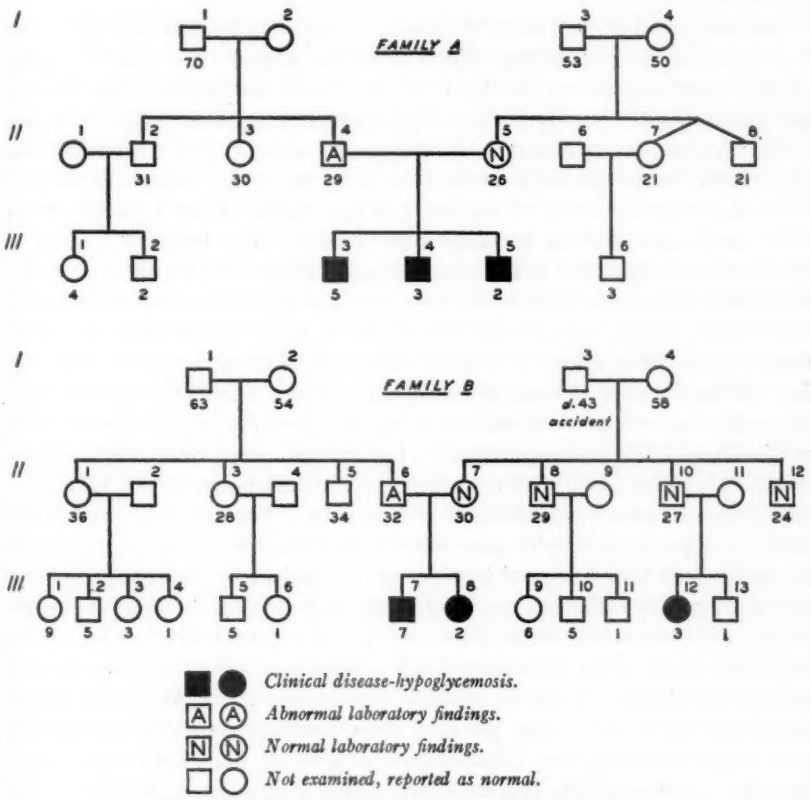

FIG. 1. Two families exhibiting spontaneous hypoglycemosis.

The overt attacks of hypoglycemia in these patients, which became manifest in each child during the first year of life, occur intermittently at intervals of a few days to a week or more. They are characterized clinically by tremors, twitching, sweating, irritability, unsteadiness, and occasional convulsions. During such episodes the fasting blood sugar values vary between 10 and 35 mg. per 100 cc. The strabismus also is accentuated at these times.

As indicated in the pedigree chart, both parents were subjected to various tests. The father was found to have an abnormal response to the insulin sen-

sitivity test. His fasting blood sugar value was 60 mg. per cent. Subsequent to the injection of insulin (0.5 unit insulin per kg. of body weight), blood sugar readings were 20, 28, 36, 42, and 48 mg. per cent at 30, 60, 90, 120, and 180 minutes, respectively. Other clinical and metabolic data obtained from studies on the three affected siblings have been more fully described elsewhere (McQuarrie *et al.*, 1949).

Affected members in Family *B* (figure 1) include a brother and sister, and a cousin. The symptomatology differs in certain respects from that in Family *A* and varies also among the different members of the family. Thus, the two affected siblings in Family *B* showed a persistently low blood sugar, with rare or no spontaneous remissions. In both cases, subtotal pancreatectomy was performed. Careful palpation at the time of operation and biopsies of the pancreas showed no evidences of tumors or of hyperplasia of the beta cells. However, microscopic sections prepared with Gomori's stain revealed decrease in the number of alpha cells in the islands of Langerhans (McQuarrie *et al.*, 1950). The older of the two children, the boy, who suffered for several critical years from severe hypoglycemia and convulsions, is markedly retarded in mental development, while his sister, treated early with adrenocorticotropic hormone, falls within the normal range of intelligence. Both suffered from severe hypoglycemia with recurrent episodes of convulsive seizures, despite special diets and subtotal (85%) pancreatectomy, but are now controlled effectively by semiweekly injections of pituitary adrenocorticotropic hormone (ACTH). Their cousin has shown a much different clinical course. She exhibited periodic attacks of hypoglycemia with generalized convulsions formerly, but has subsequently been kept free from hypoglycemic reactions by the routine use of a high-protein, low-carbohydrate, medium-fat diet. Among the relatives in this family, only one was found to show any deviation from normal as far as carbohydrate metabolism is concerned. This was the father of the two affected siblings. He showed merely an increased insulin sensitivity. While the fasting blood sugar value was 73 mg. per cent, the concentrations at 30, 60, 120, 180, and 240 minutes after the insulin injection were 30, 35, 29, 68, and 76 mg. per cent, a curve similar to that of the father in Family *A*. Except for the three affected children, no other members of the family have been known to have any signs or symptoms of hypoglycemosis.

DISCUSSION

Numerous metabolic diseases, such as diabetes mellitus, porphyria, gout, and Gaucher's disease are known to be in large part genetically determined. The occurrence of spontaneous hypoglycemosis among siblings is therefore not surprising, and is very suggestive of genetic etiological factors. Hypoglycemia *per se* is of course merely a sign of disease, and does not represent the

same disease in all cases. It can occur from insulin overdosage in any person, or in association with liver disease, pancreatic islet tumors or hyperplasia, adrenal insufficiency, anterior pituitary insufficiency, severe renal glycosuria, inadequate glucose absorption, and in other less well understood disease states. The present cases, however, do not fit into any heretofore defined category other than "spontaneous hypoglycemia" or "idiopathic hypoglycemia." In two of the patients there is microscopic evidence of a deficiency in the alpha cells of the pancreatic islands, which cells are now suspected of secreting a hormone having a glycogenolytic action. This observation suggests that the condition present in these patients may represent a hitherto undescribed endocrinological entity.

It is well known that in newborn infants the carbohydrate regulatory mechanism is often poorly developed. This fact is probably of considerable significance to the present discussion. Thus, functional hypoglycemia may occur transiently and go undiagnosed. Severe spontaneous hypoglycemia may occur transiently in the first days or weeks of life and then regress spontaneously. We have observed a number of such cases. This is the opposite of what is ordinarily observed in genetic metabolic diseases. Thus, in diabetes mellitus the clinical appearance of the disease in the genetically "susceptible" individual is largely a function of age, with the incidence increasing with age. That the reversed tendency would complicate the usual methods of genetic "ascertainment" is obvious. Thus, if infants with hypoglycemia improved with age, then tests in later life might well be normal. Such individuals would presumably have to be followed from early infancy in order to demonstrate genetic patterns. This complicated age-manifestation factor is emphasized inasmuch as it bears on the two families studied. Thus, in the examination of relatives of affected children, only two individuals were found with any deviation from normal, and these deviations occurred only on the level of subclinical laboratory findings. That they occurred among the parents of affected individuals is of considerable interest, however.

One could theorize at great length upon possible genetic mechanisms behind the appearance of spontaneous hypoglycemia in siblings. The simplest explanation is that of a recessive trait, with some heterozygous carriers demonstrable by laboratory test. However, it does not seem fruitful to go beyond this statement, except to state that there is no suggestive evidence of sex-linkage. The clinical differences of the disease in the two pedigrees shown are sufficient to warrant caution in ascribing common genes or precipitating factors. It does, however, appear probable that familial hypoglycemosis occurs and that this disorder has an hereditary basis. Further work on possible genetic mechanisms in the development of hypoglycemia is clearly needed.

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The Action of Selection on the Principal Rh Alleles

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INTRODUCTION

HALDANE (1942), and later others (e.g., Strandskov, 1945; Stern, 1949), have pointed out that natural selection would be expected to affect the frequencies of the Rh blood group genes because of the occurrence of erythroblastosis fetalis. This pathological and often fatal condition results from the isoimmunization of a pregnant woman who lacks an Rh (or Hr) antigen which the fetus carries on its red blood cells. Although at least ten such antigens are now known (C, C^w, C^u, c^v, c, D, D^u, d, E, e), yet nearly 90 per cent of erythroblastosis fetalis results from isoimmunization by D (Rh_o). A certain proportion of offspring perishes from the destruction of erythrocytes by the antibodies produced by the mother. If D is the antigen concerned, the genotype of the mother must be *dd* for this to happen, and every such offspring killed must be heterozygous (*Dd*), since the mother herself can supply the offspring only with a *d* gene. This simultaneous elimination of a *D* and a *d* gene from the population works to depress the frequency of the rarer allele. To illustrate, a loss of one gene of each sort from a group of ten genes, 6 of which are *D* and 4 of which are *d*, leaves the ratio of *D*:*d* at 5:3 or 37.5% *d*, instead of 40% *d* as before. In a population of many *D* and *d* genes, the same differential would work against the rarer allele, but of course more slowly.

The *d* gene has a frequency of 39.5 per cent in the white North American population; *D*, of 60.5 per cent (calculated from 12,140 individuals typed at the Baltimore Rh laboratory, 1945–1946; Sacks, *et al.*, 1947; see also Rife, 1948; Ottensooser & Pasqualin, 1949). The frequency of *d* in England (40.4%) and in other western European countries is not very different (Race, *et al.*, 1948). Selection would therefore be expected with the passage of time to lower the frequency of *d* (Rh negative) and to raise that of *D* (Rh positive).

An assumption implicit in these considerations seems to have been overlooked, namely, the assumption that the Rh-negative women actually produce fewer living children than the Rh-positive women. If, for any reason whatever, the Rh-negative women were to equal the Rh-positive women in number of living children, and assuming that a certain number of deaths from erythroblastosis fetalis actually occurs, this would mean that the Rh-negative women had replaced defunct *Dd* children by normal *dd* children. The net effect would

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be to increase the gene frequency of *d*, rather than to decrease it. The possibility that this might occur has, in fact, been suggested by Fisher (see Race, 1944) and Spencer (1947).

In earlier times, or wherever the pattern of family size is large, the situation just sketched would probably be impossible. As the number of pregnancies per woman increased, Rh-negative women would fall farther and farther behind the Rh-positive women in the number of surviving children. On the other hand, there prevails today in the Western world a pattern of very small family size, and such a pattern should make it no longer difficult for Rh-negative sensitized women either to reach the typical family size before losing babies through erythroblastosis fetalis, or else to replace the losses of *Dd* infants by unaffected *dd* children. Only in the case of Rh-negative immunized women married to homozygous *DD* men would the latter course be virtually impossible. Yet even these women would in most cases be able to achieve the typical family size. Thus, the net reproductive rate of cities of 100,000 or over in the Middle Atlantic States of the U.S.A. is stated to be 0.75, which means that on the average each woman in such a community has only 1.5 children who reach maturity. Since it has been found (Glass, 1949) that 54.4% of the Rh-negative women eventually immunized are not yet sensitized in their second pregnancy, 32.9% not yet in their third, and 19.3% not even in their fourth, it appears clear that relatively few Rh-negative women would experience any difficulty, due to erythroblastosis fetalis, in having two or three children.

DIFFERENTIAL REPRODUCTIVE RATES OF RH-POSITIVE AND RH-NEGATIVE WOMEN

This reasoning suggested that an actual comparison of progeny size of Rh-positive and Rh-negative women should be made. For statistical purposes it would of course be ideal if the study could have been limited to women whose reproductive period was ended; but this would have introduced variability due to mortality occurring among their children. Also, the available data would not permit this. Instead, all Rh-negative women within the child-bearing age who were typed by the Baltimore Rh Typing Laboratory during a two-year period were included. The control group was composed of a considerably larger number of Rh-positive women selected at random from the cases also typed within the same two-year period. For any women who returned to the laboratory within the given period because of a second pregnancy, only the initial record was used, since it seemed highly probable that a far larger proportion of Rh-negative women than of Rh-positive women would in fact return. That is, all Rh-negative women except those married to Rh-negative husbands might be expected to return for retesting if newly pregnant, whereas the Rh-positive women, having once been typed and assured that they would experience no

encounter with erythroblastosis fetalis, would not come back. By the procedure chosen, the danger of bias through unequal sampling of the two groups of women was avoided.

Because with the passage of time the proportion of primigravidas typed at the laboratory has increased and conversely the proportion of multigravidas has decreased, only those data collected during the early operation of the laboratory might be expected to yield a random sample of the women throughout their reproductive period. The records used were therefore those of the period August, 1945 to August, 1947, the first two years of operation of the laboratory. The unique quality of this sample should be emphasized. No future collection of data at the Baltimore Rh Typing Laboratory nor any other within the same locality can be expected to provide a true cross section in time of the female population within the reproductive period, inasmuch as future

TABLE 1. PREGNANCIES AND LIVING CHILDREN OF RH-POSITIVE AND RH-NEGATIVE WOMEN

GROUP OBSERVED	NUMBER OF WOMEN	PREGNANCIES	LIVING CHILDREN
Whites: total	8,421	15,406	11,856
Rh+	5,048	8,971	6,954
Rh−: total	3,373	6,435	4,902
non-sensitized	2,946	5,385	4,210
sensitized	427	1,050	692
Negroes: total	2,723	7,720	6,444
Rh+	2,148	6,153	5,182
Rh−: total	575	1,567	1,262
non-sensitized	508	1,326	1,066
sensitized	67	241	196

typing will be limited more and more to primigravidas and become more and more biased through the inclusion of a higher proportion of multigravida Rh-negative women than of multigravida Rh-positive women. That this predicted trend is actually taking place is shown by the fact that in the latest published report of the Baltimore Rh Laboratory (Sacks, *et al.*, 1949), the proportion of Rh-negative white women typed during the entire period of 3 years and 3 months from the initiation of the laboratory has risen to 17.48 per cent, in a total of 43,165 white persons. Unless, therefore, some other laboratory can provide a sample of comparable magnitude from a previously untyped population, the present study will have to stand alone.

Because of the generally recognized differences in family size between negroes and whites and also because of the significantly different proportions of Rh-positive and Rh-negative persons in these racial groups (see Potter, 1947; Ottensooser & Pasqualin, 1949; Sacks, *et al.*, 1949), the data for negroes and whites have been kept separate. However, the negro group is in each category

that which was found at random within the total group of all women for the period studied and the Rh type in question. Table 1 summarizes the raw data. Table 2 compares pregnancies per woman, living children per woman, and living children per pregnancy. Among both white and negro women, the mean number of living children per pregnancy is less for the Rh-negative women than for the Rh-positive women. This is in accord with the expectation based on the knowledge that erythroblastosis fetalis does account for the death of some children of Rh-negative mothers. The differential for the negro women (0.037) is greater than for the white (0.013), a fact which reflects the poorer obstetrical and pediatric care received as a rule by women and infants of the lower economic groups, to which most negroes in Baltimore belong, and the

TABLE 2. MEAN NUMBERS OF PREGNANCIES AND LIVING CHILDREN OF RH-POSITIVE AND RH-NEGATIVE WOMEN (WITH STANDARD ERRORS OF MEANS)

GROUP OBSERVED	MEAN NUMBER PREGNANCIES	MEAN NUMBER LIVING CHILDREN (PER WOMAN)	MEAN NUMBER LIVING CHILDREN (PER PREGNANCY)
Whites			
Rh+	1.777 ± 0.017 †	1.378 ± 0.016 ‡	0.775
Rh−: total	1.908 ± 0.023	1.454 ± 0.020	0.762
non-sensitized	1.83	1.43	0.78
sensitized	2.46	1.62	0.66
Negroes			
Rh+	2.865 ± 0.048 ¶	2.412 ± 0.042 §	0.842
Rh−: total	2.725 ± 0.085	2.195 ± 0.074	0.805
non-sensitized	2.61	2.11	0.81
sensitized	3.6	2.92	0.814

† $t = 4.65$, $P < 0.001$ ‡ $t = 3.05$, $P < 0.01$
¶ $t = 1.35$, $0.10 < P < 0.20$ § $t = 2.41$, $0.01 < P < 0.02$

consequently higher mortality among the children when erythroblastosis fetalis does occur, as has been previously reported (Sacks, *et al.*, 1949). The mean number of pregnancies is also lower among the Rh-negative negro woman than among the Rh-positive negro women, although the small difference is not significant for a sample of this size. The data for the negro women therefore conform to the principle described by Haldane, and one may conclude that in this element of the population the *d* gene is indeed being eliminated by selection directed against the heterozygote.

For the white women, the situation is reversed. The mean number of living children per woman is greater for the Rh-negative women than for the Rh-positive women (difference significant at the 1% level). This is clearly due to the marked difference in the mean number of pregnancies per woman in the two groups, a difference significant at the 0.1% level, and especially attrib-

utable to the high number of pregnancies per woman in the sensitized Rh-negative women. Among the white women, therefore, the *d* gene is not being reduced in frequency, but would appear to be on the increase at the expense of its *D* allele. Since the difference in mean number of living children and the difference in mean number of pregnancies per woman are clearly far higher in the negro women than in the white women, it seems logical to relate the complete reversal in the action of selection upon the heterozygote to size of family. Where family size is large (negro group), selection against the heterozygote operates so as to reduce the frequency of the rarer allele. But where family size is small (white group), compensating factors may shift the differential rates of reproduction so as to favor the rarer allele.

DISCUSSION

A question at once arises from the data just presented, namely, why do the Rh-negative white women in fact outclass the Rh-positive white women in number of pregnancies and consequently in number of living children? One suspected source of error may be ruled out. If there were different frequencies of the Rh-positive and Rh-negative types in different economic classes of the white population, such that relatively more Rh-positive individuals occurred in the higher economic groups and more Rh-negative individuals in the lower economic groups, then the well-known higher reproductive rate of the latter would produce a spurious increase in family size in the Rh-negative group. It was impossible to check this for the precise sample studied, for no information regarding the economic status of the cases had been recorded. But a sample from a later period of the laboratory's operation was available through a study made by Dr. Christopher Tietze of 3215 women, primiparas excluded. The husbands of the women typed were classified into six occupational categories (professional, business, skilled workers, semi-skilled workers, laborers, and "others"). In all of these classes the Rh-positive and Rh-negative types were in good agreement with expectation, the largest deviation being in the category of "other" professions than the five specific classes. $\chi^2 = 8.77$; D.F. = 5; $0.20 > P > 0.10$. It therefore seems unlikely that there is any real difference in the *Rh* (*D*) frequencies in different economic levels of the white population studied.

The remaining plausible explanation would appear to be that the loss of children through erythroblastosis fetalis, either as stillbirths or as postnatal fatalities, may serve to motivate parents, particularly the mothers, to replace them. As Fisher (see Race, 1944) and Spencer (1947) have suggested, families tend to fill up to a certain average size for a given population or stratum within a population. It may even be that this increased motivation to childbearing might lead to over-compensation. That is, such women might end

up by having more living children than those who have not lost children. For any group in which the average size of family is small, this would be relatively easy.

There is some evidence apart from the present study that such a situation may occur. In a study of acholuric jaundice, Race (1942) found that persons with this semi-dominant condition, which causes significant losses of infants, nevertheless "had more live children than their normal sibs." Twenty-one acholuric men and women had 37 living offspring in spite of having lost 18 offspring through postnatal death or miscarriage. Their 15 normal sibs had 19 living offspring and had lost none. The excess of living children over and above those of their non-affected sibs was more characteristic of females with acholuric jaundice than of the males, as the following calculation of the number of living children per parent shows:

acholuric males	2.1
normal males	2.0
acholuric females	1.45
normal females	0.78

The data, of course, are not extensive enough to warrant the attribution of statistical significance to the difference. It may well depend upon the inclusion by chance of a group of non-acholuric women of unusually low fecundity. Nevertheless, the facts show that it is not impossible for women with such a handicap to produce in spite of it more living children than their normal sibs.

A further example of higher fertility on the part of individuals who lose children through the action of natural selection has recently been published by Silvestroni, *et al.* (1950). In the district of Ferrara, Italy, where the frequency of microcytemia (thalassemia) is over 10%, the gene appears to be maintained in the population by the higher fertility of $Mm \times Mm$ matings, in spite of the lethality of the homozygous (MM) condition. The data reported were as follows:

MATING	NUMBER MATINGS	AVERAGE NUMBER CHILDREN	AVERAGE NUMBER LIVING CHILDREN
$mm \times mm$	1,170	3.60 ± 0.087	3.14
$Mm \times mm$	269	3.62 ± 0.17	3.03
$Mm \times Mm$	19	5.89 ± 0.96	3.26

Because of the small numbers of recorded matings involving heterozygotes, the statistical significance of the difference is questionable, but it parallels the phenomenon reported by Race for acholuric jaundice and the data on erythroblastosis fetalis reported here. This evidence therefore tends to support the explanation applied to the data of the present study, namely, that the Rh-negative women who lose offspring through erythroblastosis fetalis experience

an increased motivation to have additional children, as Fisher suggested (see Race, 1944). This leads them, consciously or unconsciously, to "fill up their families" to that size characteristic of their group or stratum in the population, insofar as this is possible. If the standard size of family in their element of the population is low, they may over-compensate for their losses and as a group actually exceed the standard size of family. This is what seems to be happening among the white women of Baltimore.

Let us now consider the influence of the differential reproduction rates upon the gene frequencies of *D* and *d*. It is a matter of record that the average size of family (number of living children) in the population of the United States has decreased rather steadily since 1810 (see Lorimer & Osborn, 1934, p. 17), declining by somewhat more than one-half in the last hundred years. Consequently the prevailing pattern of family size in Baltimore and other large cities did not reach that level which permits the Rh-negative women readily to exceed the Rh-positive women in differential reproduction rate, until a generation or two ago. Moreover, this pattern of low family size prevails only in urban communities with a population of 26,000 or more (National Resources Committee, 1938; 16th Census of the U. S., 1944). In rural areas and smaller cities and towns, where the net reproductive rate is still 1.0 or above (approximately equivalent to 2 living children per family), the Rh-negative women perhaps do not equal the Rh-positive women in the reproductive rate. The situation found to exist at present in the Baltimore white population is unlikely to have had, until now, any marked influence upon Rh gene frequencies in the population of the United States, even if the same differential be assumed to prevail in other large urban centers. Nevertheless, the differential is so great that, if maintained, it should have a considerable effect on the Rh gene frequencies in the future, especially if the net reproductive rate in rural areas and of all elements of the population continues to approach that of the white urban portion of the population. This will be clear from the following considerations. Let us assume, to be conservative, that Rh-negative women merely equal Rh-positive women in reproductive rate. Then the displacement of Rh-positive by Rh-negative genes in the population must equal the number of heterozygous fetuses and infants eliminated by erythroblastosis fetalis and replaced by Rh-negative children. This frequency may be estimated in two independent ways.

First, the frequency of fatal erythroblastosis fetalis may be calculated from clinical records. The Baltimore Rh Laboratory has reported a general incidence of 1 case of erythroblastosis fetalis per 170 deliveries in a total of 28,551 deliveries, in their 2-year survey (August, 1945 to August, 1947, unpublished). In 53.8 per cent of 119 patients, the condition proved fatal. The combination of these statistics gives a minimum value of 3.2 deaths per 1000 births. Potter (1947) has given the incidence of hemolytic disease at the Chicago Lying-in

Hospital in 1944 as 1 in every 150 births, and Diamond in 1945 also reported an incidence of 1 in 150 births. Potter also gave a figure for the mortality of 64.8 per cent (1/392:1/252). From these statistics a figure of 4.3 deaths per 1000 births may be calculated.

These values for the mortality from erythroblastosis agree very well with that assumed by Haldane (1942) as the basis of his calculations of selection against the *Rh* heterozygotes,[1] namely, $k = 0.05$. For close to 10 per cent of all births are *Rhrh* heterozygotes born to *rhrh* mothers: 0.366 *RhRh*; 0.478 *Rhrh*; 0.156 *rhrh* genotypes in the American white population, giving $0.156[0.366 + \frac{1}{2}(0.478)] = 0.0944$. Hence k, the mortality from erythroblastosis fetalis among these *Rhrh* heterozygotes born to *rhrh* mothers, must be approximately ten times as high as it is in the general population. It must be kept in mind that the frequency of a fatal conclusion was even higher in the period before effective transfusion for saving the erythroblastotic infant had come into general practice, just as it has become even lower since the period studied. Our figures at the Baltimore Rh Laboratory indicate that the present mortality rate from erythroblastosis fetalis is almost exactly 33.3 per cent of those affected. This would mean about 2 deaths from this cause per 1000 births.

The second method of determining the frequency of loss is to take the difference in the mean number of living children per pregnancy for the Rh-positive and Rh-negative groups of women. These data are given in table 2. The mean number of living children per pregnancy is smaller in Rh-negative white women by a value of 13 children per 1000 pregnancies. (For the Rh-negative negro women it is smaller by a value of 37 children per 1000 pregnancies.) This value is somewhat larger than one per cent, but perhaps not significantly so. Comparing the two independent reckonings, the loss from erythroblastosis fetalis may be estimated as about 1.0 per cent. This value is double that assumed by Haldane. Replacement of Rh-positive by Rh-negative genes at any such rate as this would require but few generations to bring the two genes to an equal frequency, particularly since, as the frequency of the Rh-negative type in the population rose, the frequency of hemolytic disease would increase, and consequently the replacement of Rh-positive by Rh-negative types would be accelerated. The process of replacement would theoretically continue to accelerate, as Haldane (1942, p. 337, fig. 2) has shown, until the gene frequency of *d* has become 0.8202, i.e., until the population consists of 67.3 per cent Rh-negative and 32.7 per cent Rh-positive persons. Before this point has been reached, the frequency of erythroblastosis fetalis would already have

[1] Throughout this note the term 'Rh-positive' has been used in the usual sense of "clinically Rh-positive," i.e., cells containing antigen D or Rh_o. Also, when referring back to early papers, such as Haldane's (1942), the original gene symbol ***Rh*** is retained; it is, of course, equivalent to *D* in the present Fisher-Race nomenclature or to ***any one*** of the alleles producing antigen D in Wiener's symbolism, i.e., R^1, R^2, R^0, or R^z.

reached its maximum, when the gene frequency had reached the values 0.667 *d* and 0.333 *D*. The height of this maximum depends only on (1) the frequency of *d*, and (2) the frequency of loss of *Rh* heterozygotes (*Dd*) and their replacement. If the present mortality from erythroblastosis fetalis is indeed around one per cent of all births, the current trend leads to a prediction of an increase of about 50 per cent in its incidence. That is, it will rise to 1.48 per cent; or 15 deaths per 1000 births. Only thereafter could it be expected to decrease. On the other hand, if we take into account the reduction in mortality from erythroblastosis fetalis likely to ensure from the full application of medical measures, *k* should be reduced to about one-half of its former value. In other words, the efforts of medical science to save erythroblastotic infants by measures known at present are just about effective enough to counteract the predicted rise in mortality because of the increase in frequency of the *rh* gene in the population. Like an animal running on a treadmill, our strenuous efforts will just maintain the status quo.

Thus we may conclude that, although the prevailing situation can throw little light on the past history of the Rh gene frequencies, it promises to have considerable importance for the future, unless in some way the current trend be reversed.

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SUMMARY

If the action of selection against Rh heterozygotes is as described by Haldane, it must reduce the gene frequency of that allele which is less common in the population, namely, *rh*. This should be evident in a lower number of living children per Rh-negative mother than per Rh-positive mother. For if the number of children is the same in these two classes, it signifies that losses of erythroblastotic heterozygotes have been equalled by births of additional viable children, i.e., *rhrh* homozygotes. The net result would be to increase the gene frequency of *rh* at the expense of *Rh*.

Number of living children has been tabulated for the two classes of women in the Baltimore population, and for whites and negroes respectively. Among the negro women, who have on the average a larger family size than white women, the relations are as predicted by Haldane: mean number of living children of Rh-positive women, 2.41; of Rh-negative women, 2.20. Among the white women the relationship is the reverse: Rh-positive women, 1.37 living children; Rh-negative women, 1.453 (difference significant at 1 per cent level). This difference is accounted for by a significantly higher number of pregnan-

cies (8 per cent increase) among the Rh-negative women. It follows that for the white population studies, selection is actually increasing the gene frequency of *rh*.

This situation, which does not prevail in the negro population studied, is most to be expected where effective control over family size exists and in those groups within which a pattern of very small size of family has been established. It is not likely to have existed for more than a generation or two in the past, although Fisher thinks otherwise; but it may reasonably be expected to become more prevalent in the future. The frequency of fatal erythroblastosis fetalis may consequently be expected to increase, if untreated, to a maximum of about 15 per 1000 births (1.5 per cent) in such urban U. S. populations as that studied, or in the general population to the extent that the pattern of small family size becomes more universal.

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BOOK REVIEWS

An Introduction to Population Genetics

By Ching Chun Li (National Peking University, Peiping, China) Peiping: National Peking University Press, 1948. Pp. viii + 321 with 7 text figures. Distributed by Oregon State College Cooperative Association, Box 491, Corvallis, Oregon.

With the growing interest in population genetics shown by students of animal and plant breeding and evolution, as well as by human geneticists, there has come to be a great need for an elementary exposition of the subject. Professor Li's excellent book serves this need and at the same time is detailed enough to be used as a reference source. Here is collected, much of it for the first time in book form, a surprising amount of the work of Wright, Haldane, Fisher, and others, and all presented with great clarity and simplicity.

The first chapter begins with the distribution of phenotypes in small segregating families and thus introduces a brief consideration of the binomial and multinomial distributions. Following this the methods developed by Lenz, Hogben, Haldane, and others for dealing with the proportion of recessive children from dominant parents are presented. The sib method of Weinberg, however, is not given. Next are seven chapters devoted to the distribution of genes and genotypes in randomly mating populations. Included are a thorough discussion of the Hardy-Weinberg equilibrium and numerous applications to problems in gene-frequency analysis, multiple alleles with particular attention to human blood group factors and self-sterility alleles in plants, sex-linked factors and their characteristic oscillatory approach to equilibrium, autopolyploids, and a chapter devoted to the equilibrium attained by two pairs of factors and the effect of linkage on its rate of attainment. Following these are six chapters on the effects of inbreeding. Self fertilization is considered first for one or several factors followed by a discussion of brother-sister mating in the manner of Haldane. Then Wright's method of path coefficients is developed and applied to various systematic mating systems as well as to the determination of coefficients of inbreeding and relationship in irregular pedigrees. After a brief treatment of assortive mating, the remainder of the book is devoted to mutation, selection, and migration and their joint effects with population size in determining the distribution of gene frequencies in an evolving population.

From this account of the contents it can be seen that the book deals largely with the distribution of a single set of alleles. There is no mention of multiple factors, the principal topic of Mather's "Biometrical Genetics," and there is no discussion of isolates, one of the principal topics in Dahlberg's "Mathematical Methods for Population Genetics." The three books, despite somewhat similar titles, have very little similarity in content or approach.

However, Professor Li's decision to limit his subject matter was probably wise, for it permits a more thorough treatment of each topic. The great merit of the book is the ease with which it can be understood by the reader with limited training in the field. This is accomplished by presenting the material slowly, with no algebraic steps left out, and very clearly. The general manner of presentation of a subject is usually the same as that of the author who originally developed it, although occasionally a new approach is introduced. The author's usual procedure is to take the original presentation and fill in the steps which in the interest of brevity were omitted in the original publications. As a result the presentation is often pedantic and rarely elegant, but for the intended reader this is a distinct advantage.

In addition to the clear derivations, each principle is illustrated by one or more numerical examples. These are well chosen, both from the standpoint of their intrinsic interest and their suitability for illustrating the principle being considered. Furthermore, there are several instructive problems at the end of each chapter. These should be especially appreciated by those beginning the field (and probably by many others as well).

This book can be read by anyone with a knowledge of elementary genetics, algebra and some knowledge of the calculus. Whenever any aspect of mathematics not conventionally taught in elementary courses is introduced (for example, recurrent series and linear transformation sets) the subject is fully explained. Particularly welcome to many readers will be the clear exposition of Wright's important method of path coefficients. The presentation is only slightly different from Wright's original articles but the author has obviously spent much effort in making the subject understandable to the beginner. The author often treats a topic two or more times, first as a simple example done directly and later as a special case of a more general method. An example is that of correlation between siblings. This is first worked out algebraically for a randomly mating population and later done by the method of path coefficients. This procedure adds greatly to the ease of comprehension of abstract principles.

The book could possibly be criticized on three grounds. (1) In his effort to be clear to the beginner the author has occasionally oversimplified a result or failed to state the limitations of a formula. Example: the formula on page 219 for the proportion of homozygous recessives whose parents were first cousins assumes that cousin marriages occur with approximately random frequency. (2) In some cases the formulae could be stated in more general form. Example: Some of Wright's equations are presented more generally in his recent publications. (3) Some of the methods given are not the best. Example: The maximum likelihood method for analysis of blood group frequencies might have been given instead of that of Bernstein. Nevertheless, in my opinion the author made the right choice. To have remedied any of these would have made the book harder for the beginner, and, as its title indicates, it is intended as an *introduction* to the subject.

There are several typographical errors, some misspellings, and an occasional sentence that gets tangled up, but none of these is such as to cause any confusion in the mind of the reader. One sentence may be misleading, however. On page 43 there is the statement: "This formula applies equally well if we use percentage frequencies ($N = 1$) instead of actual numbers." The beginning reader should perhaps be warned that when he applies this formula to data expressed as proportions he should nevertheless substitute the number in the sample (and not 1) for N.

In short Dr. Li has written a detailed and unusually clear account of population genetics that deserves to be read by all students of the subject.

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Normal Values in Clinical Medicine

By F. William Sunderman, M. D., Ph. D., Professor of Experimental Medicine and Clinical Pathology, University of Texas Postgraduate School of Medicine, and Frederick Boerner, V. M. D., Late Associate Professor of Clinical Bacteriology, Graduate School of Medicine, University of Pennsylvania. 845 pages with 412 tables and 237 figures. Philadelphia and London: W. B. Saunders Company, 1949. $14.00.

The preface of this excellent reference work begins with an apt quotation from Lord Kelvin, "When you can measure what you are speaking about and express it in numbers, you know something about it; when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind." The authors, with the assistance of 44 collaborators (all but two from the Philadelphia area) have attempted to collect into one volume as much as possible of the vast store of determinations of normal values useful in clinical medicine. A systemic form of presentation is used, with sections (each consisting of from 2 to 12 chapters) on the circulatory system, blood, blood chemistry, respiratory system, digestive system, nervous system, urinary system, male and female reproductive systems, skeleton and muscles, skin, eye, ear, nose, endocrines, metabolism, anatomical normals, teeth and saliva and miscellaneous data. The form of presentation is excellent, with clear and concise text presentation, but with all possible data on measurements presented in tabular form. The sources of the findings summarized are cited, and the extensive bibliographic references given at the end of each chapter are quite valuable. The variety of measurements made on normal persons is surprising in its scope, and includes everything from the commonly used clinical determinations to such things as measurements, with a hydraulic gnathodynamometer, of the biting force between individual opposing teeth. Wherever possible, variations in normal values that occur with age, sex or other pertinent factors are given. The work is apparently quite up-to-date, even including a 5-page table of the properties of 98 cyclotron-produced radioisotopes. An excellent index, covering 27 pages, contributes greatly to the ease with which the volume may be used for reference.

It is most unfortunate that one of the authors, Dr. Boerner, did not live to see this work in print. The reviewer feels that the book will be a most welcome addition to the general reference works available, and may serve as a fitting monument to the industry and thoroughness of the authors.

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Osteogenesis Imperfecta

By Knud Stakemann Seedorff. *Opera ex Domo Biologicae Hereditariae Humanae Universitatis Hafniensis*, Vol. 20. Copenhagen: Ejnar Munksgaard, 1949. Pp. 230 + 112 figures, 6 tables and 55 pedigrees. Price: Dan. kr. 12.—

This monograph, written in English with a Danish summary, represents an extensive investigation of the clinical and genetic features of osteogenesis imperfecta, as found in 55 Danish families including 180 affected individuals. The clinical description of the signs and

symptoms of the disease is excellent. The author distinguishes three clinical types: Osteogenesis imperfecta congenita (Type I) is described as characterized by multiple prenatal as well as intrapartum fractures, and failing ossification of the skull and prenatally developed callus can be demonstrated by X-ray in the neonatal period. This is the most severe variety, and the prognosis is extremely poor. Osteogenesis imperfecta tarda is subdivided into Type II and Type III. In patients of Type II the liability to fractures is manifest at birth and tends to remain unchanged throughout life; in patients of Type III, fractures appear at about age 2 or 3 years, and the tendency to fracture declines at about the age of puberty.

The cardinal signs of the disease are blue sclerotics, bone fragility and deafness due to otosclerosis, the combination of all three being frequently described as Van der Hoeve's syndrome. Seedorff found blue sclerotics in all cases in this study, while bone fragility appeared in 84% and deafness in 26%. The combination of blue sclera and bone fragility occurred in 61% of cases, blue sclera and deafness in 4%, while all three cardinal signs appeared in 23%. It is noteworthy that all cases described as "affected" presenting blue sclerotics alone were in families with multiple cases; no family was included in the study unless at least one member exhibited an abnormal tendency to fracture plus blue scleras. It is not definitely stated in the text whether cases presenting bone fragility without blue scleras were purposely excluded or were not encountered; from the general thoroughness of the descriptions the reviewer assumes that such cases, although fairly frequent in the United States, were not encountered in the Danish survey. The clinical section also covers fully the secondary and less common signs and symptoms, and reviews the biochemical, radiologic and pathologic features. There is a full chapter on differential diagnosis, including an extensive listing of other diseases associated with bone fragility or pathologic fractures.

The family histories of all cases are given in detail in a separate section of 84 pages, and a pedigree diagram is given for each of the 55 families. These are subdivided into five groups: (1) 6 families in which the congenital form (Type I) occurs in a single individual (solitary cases); (2) 1 family with the congenital form and the late form (Type II) occurring in consecutive generations; (3) 28 families with solitary cases of the late form (Type II or III); (4) 9 families with the late form occurring in two generations; (5) 11 families with the late form in more than two generations. The author concludes from the data presented by groups 4 and 5 that the condition is completely dominant in inheritance and not sex-linked. The 34 solitary cases are attributed to mutation. No attempt is made to estimate a mutation rate.

The author's contribution to the genetic theory of osteogenesis imperfecta is his suggestion that the condition is not due to mutation at a single locus but may represent mutation in five closely linked or even adjacent loci. It is suggested that the gene complex may be arranged in the following order: (1) gene controlling deafness; (2) gene controlling blue sclerotics; (3), (4) and (5) three genes, designated *a*, *b*, and *c*, controlling bone fragility. It is assumed that the late form of the disease, Type III, represents mutation involving the locus for blue sclera plus gene *a* for fragility; that the late form, Type II represents mutation at the blue sclera locus plus loci *a* and *b*; that the congenital form, Type I, represents mutation at blue sclera + *a* + *b* + *c*; that Van der Hoeve's syndrome represents mutation at deafness + blue sclera + *a* + *b*. The author also states that the possibility cannot be excluded that the mutation is the same for Types II and III, and that the loss of modifying genes may determine the occurrence of Type II. It is demonstrated that both Types II and III may occur in the same family, and this is cited as evidence suggesting modifying genes. The congenital form, considered to result from mutation involving all three of the postulated genes controlling bone fragility, is regarded as a sublethal mutation.

It is unfortunate that critical data are not available which would permit differentiation between the theory of Seedorff as outlined above and the more generally accepted theory that a single dominant gene with pleiotropic effects is involved. It is obviously extremely difficult to obtain information which would permit such distinction in human families. Seedorff's theory implies that environmental factors have little if any influence on the development of the disease, and ascribes the observed clinical variations to differing genotypes. A position effect is also postulated, as it is assumed that gene *b* cannot mutate unless gene *a* has also undergone mutation, and that gene *c* does not mutate unless both *a* and *b* also mutate. An alternative explanation would be the assumption that *a* is epistatic to *b* and *b* epistatic to *c*. On the other hand, the theory that osteogenesis imperfecta is due to a single dominant gene with pleiotropic effects, variable expressivity and slightly reduced penetrance, by implication ascribes the observed clinical variations to unidentified environmental factors. It is assumed that the effects of the mutant genotype may be modified to a considerable extent and even suppressed altogether by unidentified non-genetic factors. This theory, like Seedorff's, does not exclude the possibility that the clinical variation may be influenced by non-specific modifying genes.

If one may be permitted some wishful thinking, it would seem that the single gene theory would be more attractive to clinicians and investigators than Seedorff's theory. The assumption that environmental factors may be effective in influencing the clinical expression of the disease carries the hope that further investigation may identify these factors and that they might be used as therapeutic weapons to alleviate the suffering of the unfortunate affected individuals. Such hope is largely denied by implication under Seedorff's hypothesis. It is therefore not merely a matter of academic interest to differentiate between the two theories, as final proof of the correctness of one or the other, with or without modifications, may have important practical applications to clinical medicine. The reviewer is grateful to Seedorff for the careful presentation of his findings and for pointing up this problem.

It is hoped that further investigation bearing on these questions will be stimulated by this monograph.

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